Unexplained symptoms in primary care

an integrated physical and psychological approach

Els van Westrienen

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Alone
we can do so little;
together
we can do so much.

Helen Keller

Contents

Chapter 1

General introduction

Medically Unexplained Physical Symptoms

Definition, epidemiology and prognosis

Everybody can experience physical symptoms, that may originate from every anatomical structure or bodily region and can be very diverse in severity. Most of these physical symptoms are temporary and remain unexplained [1]. If they persist they are usually first presented to the GP as isolated symptoms, such as low back pain, fatigue or abdominal pain. Still, an adequate explanation for the physical symptoms is often lacking, even after the GP consultation, and diagnostic investigations.

Multiple definitions can be used in patients with unexplained physical symptoms [2]. In this thesis the term Medically Unexplained Physical Symptoms (MUPS), Somatisch Onvoldoende verklaarde Lichamelijke Klachten in Dutch, is used. This terminology is in line with the Dutch Multidisciplinary Guideline for MUPS and Somatoform Disorders and the Dutch national guideline for general practitioners (GPs) on MUPS. In these guidelines, MUPS is defined as physical complaints that last for at least a few weeks, which are not explained by a medical condition after proper medical examination [3,4].

According to key symptoms MUPS can be classified in six clusters: 1. abdominal, 2. fatigue, 3. musculoskeletal, 4. cardiology-respiratory, 5. neurology and ear-nose-throat, and 6. other symptoms including premenstrual syndrome, dyspareunia and urinary tract symptoms [5,6]. Unexplained symptoms can be regarded as a continuum with a spectrum from mild, to moderate, and persisting or chronic MUPS. In this spectrum, mild MUPS have an estimated prevalence of 70-80% [7]. These complaints usually have a low impact, are in one or two clusters and in many patients transient. Patients with moderate MUPS have complaints more frequently and within two or three clusters. Furthermore, the symptoms have a higher impact in their daily life, and these patients more often experience psychological and physical distress [7]. The estimated prevalence of moderate MUPS is 15% in a clinical

Case of a patient with moderate MUPS

Miep van de Zee is 48 years old and has pain in her neck and lower back and experiences fatigue. Due to these complaints she consulted the general practitioner (GP) multiple times in the last year. The GP performed a physical examination and blood examination, both with normal results. Miep was referred to the physical therapist, who instructed Miep about the importance of physical activity, despite the pain and fatigue. Unfortunately she did not experience any relief, and actually the complaints got worse. This made her frustrated and she got anxious that something serious was going on, like a chronic infection or cancer. She became less active, experienced more problems with sleeping and concentration and got more anxious with negative thoughts. She felt hopeless, "will my complaints ever disappear?".

setting [7]. In chronic MUPS the impact is even higher and more clusters are involved. Patients with chronic MUPS have more severe symptoms and experience psychological and physical dysfunction [7]. Patients with chronic MUPS are diagnosed with a functional somatic syndrome (e.g. fibromyalgia, chronic fatigue syndrome or irritable bowel syndrome), or a somatic symptom disorder according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition. The prevalence of chronic MUPS is estimated to be 3-5% in a clinical setting [1,7-9].

Many patients with MUPS have a good prognosis. Fifty to 75% of the patients with MUPS improve within one year. Yet, unfortunately approximately 10 to 30% deteriorate [10]. An unfavourable course towards chronicity is expected when patients have a multiple number of physical symptoms within different clusters, experience more severe symptoms, have poorer physical functioning, have financial problems or have a history of childhood physical abuse [10,11]. Furthermore, female gender and an older age seems to be associated with unfavourable disease course, but results are inconsistent [11,12]. Having chronic MUPS has a high impact on patients' quality of life [1,13-16]. Patients with chronic MUPS often experience a lower quality of life, especially when they grow older, when they lose their job, and they have more depressive and anxiety symptoms, and more somatisation symptoms along with severe pain [17-22]. Patients with chronic MUPS consult health care professionals frequently. On average, they have 8 visits to a medical specialist, 15 GP consultations and 14 sessions with a physical therapist annually [15,23]. Despite the associated frequency of diagnostic tests, patients with MUPS do not get sustained reassurance from negative diagnostic tests [24]. Instead, they are at risk of iatrogenic harm due to the numerous and unnecessary investigations [25]. Furthermore, over 80% of the patients use almost 3 different forms of medication [15]. As a result, the inadequate use of healthcare resources and medication leads to substantial costs [26]. The mean annual healthcare-related costs for patients with chronic MUPS is estimated to be over €3.000, on average €1.000 more than the mean annual healthcare costs per patient in the Netherlands [15]. Furthermore, chronic MUPS is associated with high indirect (work-related) costs. Almost half of the patients with MUPS reported partially or fully absence from work, with estimated mean annual work-related costs of almost €2.500 [15].

Diagnosing of MUPS

In the Dutch gatekeeper system patients with physical symptoms consult their GP first. Over time, patients with MUPS may consult with unexplained symptoms from a different origin and different clusters. Timely diagnosis of MUPS therefore depends on adequate pattern recognition by the GP. However, for GPs identification of patients with MUPS is challenging and complex, for different reasons [27]. On the patients' side, communication style and presentation of symptoms may impede the identification of

MUPS [27]. Some patients are strictly focused on their physical symptoms and do not link them to psychological factors. This focus might emerge from patients' beliefs that primary care is an inappropriate setting to discuss psychological issues [27]. On the GPs' side, they frequently persist in performing new diagnostic procedures [28], because they fear to miss a serious medical illness or are reluctant to link physical complaints to psychosocial factors [27]. On the interaction side, GPs often experience frustration and stress during consultation with patients with MUPS [27-30]. Patients feel disappointed because of the persisting symptoms and the fact that their GP is unable to help them. As a result, diagnosing MUPS is a long process. On estimate it takes two years before a chronic MUPS syndrome like fibromyalgia is diagnosed with progressing symptom impact during this time period [31].

Adequate identification of patients with MUPS in Electronic Health Systems is complicated because there is no diagnostic code for MUPS in the International Classification of Primary Care (ICPC) or the International Classification of Diseases (ICD) coding system. A screening tool based on MUPS related symptoms and diseases may support GPs in the identification of patients with MUPS in primary care. Over time, two different screening tools using electronic medical record data (EMR) have been developed to identify patients with established MUPS in primary care [32,33]. Despite promising initial results both are not suitable for clinical application. Many potential patients with MUPS would be missed in the screening method of den Boeft et al. [32], while the screening tool of Tian et al. focuses on patients with chronic pain, and MUPS includes a broader range of symptoms [33].

Early identification of patients with moderate MUPS in primary care practice could prevent chronicity. Identifying patients at risk could be based on advanced analysis of routine EMR data. Proactive periodical screening of these EMR provides a quick overview of patients at risk and could support the GP in timely diagnosis by identification of patients with characteristics of MUPS. By this so called 'panel management' [34], GPs can efficiently identify and treat patients with moderate MUPS, thus preventing the transition to chronic MUPS.

Management of MUPS

According to professional guidelines, GPs have a central position in the management of MUPS [3,4,35]. Guidelines generally recommend to focus in the diagnostic process on all dimensions of the complaints (i.e. somatic, cognitive, emotional, behavioural and social dimensions), to perform a thorough physical examination and to be cautious with diagnostic investigations and diagnostic referrals. For therapy a stepped-care approach is recommended, starting with the low impact treatment. Frequently used

management strategies are information and explanation, medication, cognitive behavioural therapy, physical therapy with a time contingent approach and exercise therapy [4,28]. When there is no adequate response, the GP can intensify the treatment. In patients with mild MUPS, this included starting with providing education, addressing the perpetuating factors and creating a time contingency plan. The GP should consider to refer patients with moderate MUPS to a mental health nurse and/or physical therapist in primary care. For patients with chronic MUPS referral to a multidisciplinary intervention in secondary or tertiary care may be needed [3,4].

Much research has been conducted on interventions for patients with chronic MUPS and specific MUPS syndromes as fibromyalgia, chronic fatigue syndrome and irritable bowel syndrome [36-50]. Explanation of the complaints is an important aspect of management, particularly education on pain processing and sensitisation by the nervous system [44,45,51]. In a systematic review on neuroscience education, the authors concluded that an educational strategy addressing neurophysiology and neurobiology of pain can have a positive effect on pain, disability, quality of life, catastrophization and physical performance [45,51]. During education, the link to possible perpetuating factors of the patient can be made.

Most pharmacological interventions focused on antidepressants in patients with one of the MUPS syndromes. Conflicting evidence is found in efficacy of antidepressants and evidence for long-term effects are still lacking [23,46-50]. Furthermore, only low to very low quality evidence is available for the effectivity of new generation antidepressants and natural products [23]. Overall, no pharmacological interventions are known that sufficiently treat all symptoms while avoiding the risk of adverse events [49]. The guideline therefore recommend to be reluctant with pharmacotherapy in MUPS [4].

A commonly used, evidence based, psychological intervention to treat patients with MUPS is cognitive behaviour therapy (CBT) [37]. In systematic reviews on CBT, the authors concluded that CBT is an effective psychological treatment for patients with MUPS [37,38]. Patients who were treated with CBT experienced relief in physical complaints (e.g. pain or fatigue) and an improvement in their health-related quality of life [37,38]. Other psychological therapies have not been adequately studied [52].

Physical therapy is recommended to support patients with MUPS in staying physically active [53]. A physical activity should be gradually increased until patients should at least have 150 minutes of moderate intense physical activity every week, spread over several different days, according to the Dutch Standard for Healthy Physical Activity [54]. Furthermore, exercise therapy is demonstrated to have a positive effect on physical

complaints, health related quality of life, physical function and physical capacity in patients with MUPS [39-42,55].

Many multidisciplinary interventions for MUPS are investigated. Combining physical and mental health interventions may be more effective than monotherapy alone, since patients with MUPS are not willing to accept a psychological intervention(51). There is limited evidence that interventions, mostly combining CBT, education and exercise therapy, have a positive effect on the key symptoms for patients with MUPS [56-58]. Enhanced care is a multidisciplinary intervention where the GP provides cognitive behavioural techniques. Until now, it has not been demonstrated to have a favourable effect on patients' outcome [59].

Although much research has been performed on therapeutic interventions for MUPS, in general there is limited evidence. Furthermore, many interventions had a wide variety in duration and intensity, patients characteristics were heterogeneous, and their symptoms varied in duration, type and severity of symptoms. In addition, the vast majority of studies included patients with chronic MUPS. So far little research has been conducted in moderate MUPS, partly due to the fact that adequate identification is difficult. Early identification of patients with moderate MUPS would enable interventions directed at prevention of chronicity. A multidisciplinary intervention for patients with moderate MUPS, as part of the stepped-care approach, would be of interest, because this might prevent chronicity [52].

Blended care; the potential of digital health

The use of digital technologies is a part of our daily life, with mobile devices as smart phones, personal digital assistants and tablets. Digital technologies are also used in healthcare, for example with patients' electronic medical records, e-consults and decision-support tools. Furthermore, most patients already have Googled their symptoms before consulting a health care professional. Digital health is a broad umbrella term encompassing eHealth, which is defined as "the use of information and communications technology in support of health and health-related fields" [60].

In 2019, the World Health Organization published the first guideline on digital health interventions, indicating the substantial interest for eHealth [60]. EHealth has the potential to improve access to health care services, improve quality of care, make health care professionals work more efficiently, improve quality of life of the patients and decrease health care costs [60,61]. Despite the potential of eHealth, it also has some challenges, e.g. insufficient training, infrastructural limitations and poor access to equipment and supplies [60]. Furthermore, the use of eHealth in daily practice is complex and

implementation depends on various factors as easy-of-use, skills and knowledge of end-users, and costs. Therefore, eHealth interventions should not be a substitute of face-to-face interventions. In order to offer patients the "best of both worlds," eHealth can be integrated within face-to-face sessions, called blended care.

Blended care is promising, but also has some barriers. The most important barriers are that the online part of the intervention is not suitable for every patient, the possibility of problems with interpretation due to a lack of non-verbal communication and the lack of financial incentive [62,63]. Another drawback is the inability to monitor patients' progress between the face-to-face sessions [63]. The opportunity that patients have 24/7 access to the online part of the intervention was positively perceived. Patients can continue their treatment between the face-to-face sessions in a structured way in their home environment, which ensures continuity of care and enhance self-management with translation of the intervention into daily life [63]. Furthermore, blended care facilitates tailoring the face-to-face sessions to the individual's needs and it has potential to reduce treatment costs [63,64].

So far, there are no blended care interventions in patients with MUPS and evidence for interventions using eHealth in patients with MUPS is limited [65]. A promising blended care physical therapy intervention is e-Exercise, which is a 12-week intervention where face-to-face sessions with a physical therapist are integrated with a web-based program [66]. The e-Exercise intervention has already been investigated in patients with osteoarthritis with promising results [66]. The majority of the participants adhered to the web-based program and physical therapists were positive about the usage of e-Exercise [67]. Furthermore, physical therapists suggested to complement e-Exercise osteoarthritis with e-Exercise programs for other disorders [68].

Importance of a proactive multidisciplinary intervention for patients with moderate MUPS

In summary, there is a necessity of early identification of patients with moderate MUPS, to conduct proactive care to prevent chronicity. Panel management seems to be very promising to shift the focus of care from patients who consult the GP with their health problem (responsive consultation-based care) to the GP proactively approach patients at risk of disease, whether or not these patients seek care (proactive population-based care) [69]. Panel management has been shown to improve preventive care [70]. To address this we developed a multidisciplinary intervention with two different management strategies, focusing on promoting self-management and integrating face-to-face care with web-based components in primary care. The intervention integrates a physical and psychological intervention: the patient starts at the physical

therapist focusing on the physical complaints, and subsequently, the mental health nurse addresses the psychosocial complaints. The intervention aims to stimulate patients' self-management to recognize and adapt to symptoms in order to improve quality of life [2,71].

Aim of this thesis

The aim of this thesis is twofold: first to develop and evaluate an efficient method to adequately identify patents with moderate MUPS in primary care. The second aim is to evaluate the effectiveness of a proactive, blended multidisciplinary intervention, combining physical therapy and mental health nurse intervention in patients with moderate MUPS in primary care.

Outline of this thesis

In Chapter 2, we determined the prognostic accuracy of the PRESUME (preventive screening of medically unexplained physical symptoms) screening method in identifying patients with an increased risk of moderate MUPS. The results of this cohort study supported a more proactive panel management approach offering identified patients with moderate MUPS a preventive intervention.

In Chapter 3, the identification of treatment modalities based on expert opinions for the development of a blended and multidisciplinary intervention are described. Based on the results of the focus groups with experts and a literature search, a proactive, blended and integrated mental health and physical therapy intervention (PARASOL) was developed. Chapter 4 describes the study protocol of the multicentre randomized controlled trial study to study the (cost-)effectiveness of the PARASOL intervention in patients with moderate MUPS. In Chapter 5 common characteristics seen in patients with moderate MUPS are described and compared with characteristics seen in patients with chronic MUPS and the general population. Furthermore, we identified determinants of the physical and mental component of the quality of life in patients with moderate MUPS.

In Chapter 6, the results of the short-term and long-term effectiveness of the PARASOL intervention compared to usual care are presented. In Chapter 7 we present barriers and facilitators from patients' perspective with regards to the usability of the PARASOL intervention. Finally, Chapter 8 presents a general discussion of the entire PARASOL project and our findings, methodological considerations and recommendations for future research as well as implications for daily use. This dissertation ends with a summary in English and Dutch.

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Chapter 2

Identification of patients with moderate MUPS

Based on:
Identification of patients with moderate medically unexplained physical symptoms in primary care with a five years follow-up

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Paula E. van Westrienen,
Martijn F. Pisters, Cindy Veenhof,
Nicolaas J. de Wit

Abstract

Background

Patients with medically unexplained physical symptoms (MUPS) are common in primary care, with a spectrum from mild to moderate and chronic MUPS. The burden of chronic MUPS is high, and early identification of moderate MUPS patients is important to prevent chronicity. The PRESUME screening method to identify moderate MUPS patients in primary care was developed, but insight in prognostic accuracy is needed. Therefore, our objective is to determine the prognostic accuracy for identification of moderate MUPS patients using the screening method with 5 year follow-up.

Methods

The PRESUME screening method consists of three subsequent steps based on consultation frequency, exclusion of medical/psychiatric diagnosis and identification of MUPS. In a random 10% sample of patients from the Julius General Practitioners Network (n = 114.185), patients were identified with mild, moderate or chronic MUPS in 2008 (index year), using routine care data. In 5 years follow-up we calculated predictive values and odds ratio's for sustained MUPS related symptoms.

Results

In 2008, 789 patients (6.9% of the patient population) were identified as having mild, moderate or chronic MUPS. On average 55.5% of the moderate MUPS patients in 2008, still had MUPS related symptoms or developed chronic MUPS in 5 year follow-up. Positive predictive values for maintaining MUPS related symptoms or worsening was 67% after 1 year, and 48.7% after 5 years for moderate MUPS patients.

Conclusion

The prognostic accuracy of the PRESUME screening method using electronic medical record data for identification of moderate MUPS patients is moderate. However, it might be a useful method to identify patients at increased risk of moderate MUPS, if combined with a validity check by the GP.

Background

Medically unexplained physical symptoms (MUPS) are a serious problem in primary care [1]. Common unexplained symptoms in primary care include fatigue, pain, dizziness and general "malaise" [2]. In the Dutch multidisciplinary guideline for MUPS and Somatoform Disorders, MUPS are defined as physical complaints that last for at least a few weeks and are not explained by a medical condition after proper medical examination [3]. Of all complaints that patients present to their general practitioner (GP), 25–50% cannot be medically explained immediately [4].

MUPS can be regarded as a continuum with a spectrum from mild, to moderate, and persisting or chronic MUPS [3, 5, 6]. Seventy percent of the patients who consult their GP with a MUPS related diagnosis improve within 2 weeks (mild MUPS) [7–9]. The remaining 30% of the patients still experience unexplained symptoms after 3 months [9]. Most of them have moderate MUPS, the prevalence rate of patients with chronic MUPS (e.g. fibromyalgia, chronic fatigue syndrome or irritable bowel syndrome) in primary care is approximately 2.5% [4, 10].

Despite the low prevalence of chronic MUPS, the burden is substantial [4]. The impact on patients quality of life and daily functioning is high. Patients with MUPS have an above average consultation rate [11], and are more subject to diagnostic procedures [8]. For GPs adequate management of MUPS is challenging and often frustrating, due to the mismatch with the expectations of patients [12]. Finally, MUPS are associated with increased direct health care costs (due to higher utilization and unnecessary treatments) and indirect costs (e.g. work and insurance related costs) [11, 13].

Although previous research has identified several modifiable risk factors for the development of chronic MUPS [12, 14], GPs do not timely recognize patients with chronic MUPS [15]. It takes about 2 years before a chronic MUPS syndrome as fibromyalgia is diagnosed, without additional health benefits in the meantime [16]. Therefore, early identification of patients with increased risk of moderate MUPS is important to improve the prognosis, prevent chronicity and reduce health care costs. A screening method aiming at timely recognition of patients at increased risk of MUPS is needed. This could support so called 'panel management' [17] of MUPS in general practice, in which GPs identify patients with early stage MUPS and offer them interventions to prevent chronicity.

Recently, a new screening method (preventive screening of medically unexplained physical symptoms; PRESUME) was developed to identify patients with an increased risk of mild, moderate or chronic MUPS using electronic medical record (EMR) data (Fig. 1).

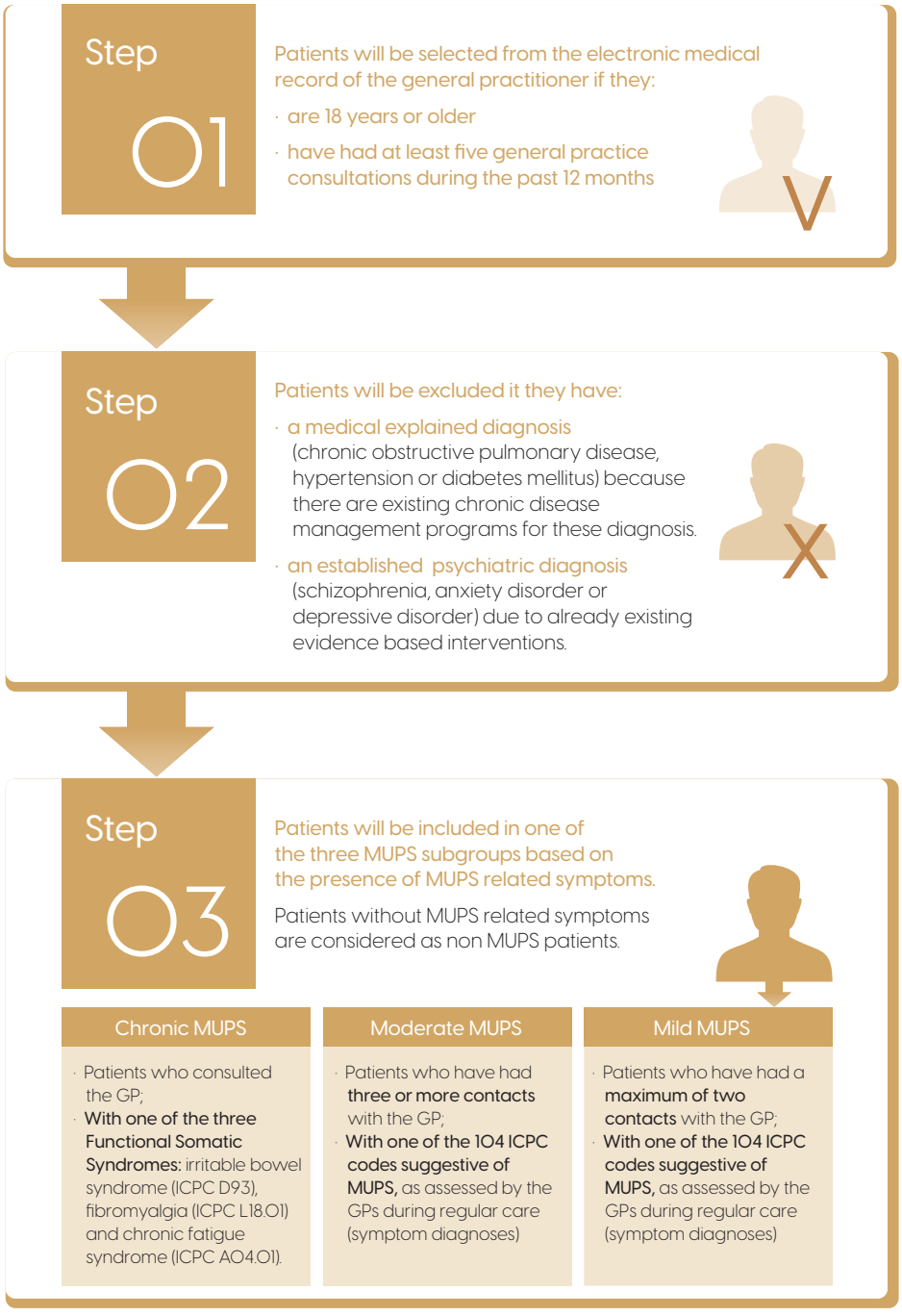

Figure 1. PRESUME screening method.

In a validation study in primary care, the screening method was compared with a questionnaire on the severity of somatic symptoms, demonstrating low sensitivity and high specificity [18]. However, this study focused only on the presence or absence of chronic MUPS. The prognostic accuracy of the PRESUME screening method for identification of patients with an increased risk of moderate MUPS remains unclear. Knowledge of the prognosis of patients with moderate MUPS is needed before the PRESUME screening method can be used for early identification of high risk patients and adequate prevention of chronicity. Furthermore, it is of interest to determine the consistency of the early identification of high risk patients by following the transition of patients between MUPS subgroups over time. Besides the transition of patients between MUPS subgroups over time, a part of the patients with MUPS will probably develop a medical or psychiatric diagnosis over time. Therefore, it is of interest to provide insight in the development of these disorders in patients of the MUPS subgroups.

Therefore, the objective of this study is to determine the prognostic accuracy of the PRESUME screening method in identifying patients with an increased risk of moderate MUPS. Secondly, transitions between MUPS subgroups for patients with an increased risk of moderate MUPS as well as transitions of MUPS subgroups to an anxiety and/or a depressive disorder or medical diagnosis over a 5 year follow-up period will be assessed.

Method

Study design

In this prognostic cohort study we identified patients with an increased risk of MUPS (mild, moderate and chronic) using historical data from electronic medical records of general practitioners, and followed them up over a period of 5 years to gain a prospective value of patients with moderate MUPS using PRESUME.

Setting and study population

This study was conducted with routine health care data as collected within the Julius General Practitioners Network (JGPN) database, which was approved by the medical ethical committee of University Medical Center Utrecht (file#99–240). JGPN comprises data from 72 primary care practices with 215 GPs in the central part of the Netherlands. This represent the average Dutch primary care practice and GP, where 49% of the GPs is male with an average age of 48 years [19, 20]. Data in the JGPN database are anonymously extracted from the EMR from participating practices, and were successfully used in different studies [21–25], which is in line with the International Ethical Guidelines for Health-related Research Involving Humans and the Dutch Law on Medical Treatment Agreement [26].

Patients who deny access to their anonymized files when joining the practice are exempted from analysis (opt out). Other patients have given consent for using their anonymized data for scientific analysis.

GPs did not receive specific training on coding, but before EMR data was extracted, all included primary care practices signed a collaboration agreement that care registration is based on the standards and guidelines that apply within the profession of the GP [27]. GPs are systematically registering a clinical diagnosis using the International Classification of Primary Care (ICPC). Furthermore, the consultations are registered according to the "SOAP system" [28].

In 2008 the database consisted of 114.185 patients between 18 and 65 years. The patient population is a representative sample of the Dutch population [29]. Four times a year, the database is updated, adding new data to the previously retrieved data. Data was obtained from the data manager of the JGPN. The data manager conducted a data check, where a prerequisite for this study was that patients who had complete follow-up data during 5 year follow-up period (2009–2013) were eligible. To get a feasible database without unduly great statistical power, a random sample of 10% of the JGPN data base in 2008 was used [30].

Patients identification

The PRESUME screening method was used to identify patients with MUPS symptoms in three subgroups according to severity and disease impact. The method is based upon three subsequent steps (Fig. 1). In the first step patients aged ≥18 with five or more GP consultations in 2008 (the index year) were selected, since high consultation rate is a key phenomenon of MUPS in general practice [4]. In the second step patients with an established medical diagnosis, who were in a chronic disease management program for chronic obstructive pulmonary disease, hypertension or diabetes mellitus were excluded. Furthermore, patients with a psychiatric diagnosis were excluded due to already existing multidisciplinary guidelines with evidence based interventions for anxiety disorders, depressive disorders and schizophrenia [31–33]. In the third step, patients were identified with an increased risk of mild or moderate MUPS, based on the presence of MUPS related symptoms (Additional file 1), or chronic MUPS, based on an established chronic MUPS diagnosis (e.g. fibromyalgia, chronic fatigue syndrome or irritable bowel syndrome). All other patients were considered as non MUPS patients.

Outcome

In order to assess the prognostic value for identifying an increased risk of sustained moderate MUPS, the index cohort (2008) were followed up for 5 years and reclassified according to the PRESUME in each follow-up year (2009–2013). Furthermore, the percentage of patients that developed a depressive and/or an anxiety disorder or a medical explained diagnosis (Additional file 2) during the 5 year follow-up period was determined.

Data analysis

Data were analyzed using SPSS 22.0 for Windows (IBM Corporation, Armonk, NY, USA). Descriptive statistics were used to describe the patient population. Differences in baseline characteristics (gender, age) between subgroups were investigated using Pearson's Chi-square and Kruskal-Wallis statistics.

For determination of the stability of the patients with an increased risk of moderate MUPS identified in the index year using PRESUME, transitions between MUPS subgroups over 5 years follow-up were determined, per year separately. It was hypothesized that at least 25% of the patients will still have an increased risk of mild or moderate MUPS (MUPS related symptoms) or developed chronic MUPS after 5 years follow-up.

To determine the prognostic value of PRESUME in predicting an increased risk of sustained MUPS diagnosis, positive and negative predictive values and odds ratios were calculated after one and 5 years follow-up. Accuracy was considered high when predictive values were > 75%, moderate accuracy with predictive values between 50 and 75% and low accuracy with predictive values < 50%.

Based on previous research [6, 34], our expectation was that at least 25% of the patients with chronic MUPS and 20% of the patients with an increased risk of moderate MUPS would be diagnosed with a depressive and/or an anxiety disorder during the 5 years follow-up. The patient was classified with a medical diagnosis if a medical diagnosis was coded during follow-up in the same ICPC chapter as the MUPS related diagnosis in the index year (Additional file 2). Based on previous research [35, 36], it was expected that less than 5% of the patients within one the MUPS subgroups will develop a medical diagnosis in the same ICPC chapter as the MUPS related diagnosis in the index year during the 5 years follow-up. Differences were investigated using one-way ANOVA statistics. To determine the prognostic risk for a depressive and/or an anxiety disorder or medical diagnosis odds ratios were calculated.

Results

Of the random sample of 11.419 patients from the JGPN database (50.6% female, mean age 41.7 years), 2.073 patients (18.2%) had more than five encounters in 2008. Of these, 35.1% (n = 729) had a medical explained diagnosis (e.g. chronic obstructive pulmonary disease, hypertension or diabetes mellitus) or an established psychiatric diagnosis (e.g. schizophrenia, anxiety disorder or depressive disorder). Of the remaining 1344 patients, 789 (58.7%) were identified with an increased risk of MUPS and classified in one of the MUPS subgroups (see Table 1). Of the total sample, 455 patients (4%) were identified in the mild MUPS group (69.9% female, mean age 41.4 years), 273 patients (2.4%) were identified with an increased risk of moderate MUPS (70% were female, mean age 41.1 years) and 61 patients (0.5%) were identified in the chronic MUPS group (73.8% female, mean age 42.5 years).

Table 1 Baseline characteristics of the study population in index year

	Study population	Chronic MUPS	Moderate MUPS	Mild MUPS	Non MUPS	Significance
	n=11.419	n=61; 0.5%	n=273; 2.4%	n=455; 4.0%	n=10.630; 93.1%	*p*-value
Female, n (%)	5.779 (50.6%)	45 (73.8%)	191 (70%)	318 (69.9%)	5.225 (49.2%)	< 0.001[a]
Mean age in years (SD)	41.7 (12.5)	42.5 (11.9)	41.1 (12.0)	41.4 (11.9)	41.8 (12.5)	> 0.05[b]

[a] *Differences between MUPS classifications evaluated with Pearson's Chi-square test.*
[b] *Differences between MUPS classifications evaluated with Kruskal-Wallis test*

Table 2 Percentages of changes of moderate MUPS patients (n = 273) in index year (2008) during 5 years follow-up

	2009 %(n)	2010 %(n)	2011 %(n)	2012 %(n)	2013 %(n)
	One year follow-up	Two years follow-up	Three years follow-up	Four years follow-up	Five years follow-up
Non MUPS	33 (90)	38.5 (105)	46.9 (128)	52.4 (143)	51.3 (140)
Mild MUPS	31.9 (87)	31.1 (85)	27.8 (76)	19.4 (53)	21.6 (59)
Moderate MUPS	34.1 (93)	26.4 (72)	18.3 (50)	19.8 (54)	17.6 (48)
Chronic MUPS	1.1 (3)	4.0 (11)	7.0 (19)	8.4 (23)	9.5 (26)

Of the patients identified with an increased risk of moderate MUPS in 2008, 46% still had MUPS related symptoms during the 5 year follow-up period, and 9.5% (n = 26) had developed chronic MUPS (see Table 2).

The prognostic value of patients identified at increased risk of moderate MUPS in 2008 was determined after 1 year and after 5 years follow-up (see Table 3). The positive predictive value (PPV) for still having MUPS after 1 year follow-up was 67%. The negative predictive value (NPV) was 82.5% after 1 year. After 5 years, the PPV was 48.7% and the NPV was 77.8%. Patients identified at increased risk of moderate MUPS have 9.8 higher odds of maintaining MUPS related symptoms or worsening in 1 year follow-up compared to patients with non MUPS. After 5 years follow-up, the odds for sustained MUPS related symptoms or progression to chronic MUPS is 3.3 times higher for patients identified at increased risk of moderate MUPS compared to patients with non MUPS in the index year.

During the follow-up period, 261 patients of the index sample (2.2%) developed a depressive and/or an anxiety disorder, of which a depressive disorder was most frequently diagnosed (n = 145; 55.5%) (see Table 4). Additionally, 109 patients developed both an anxiety disorder and a depressive disorder. Of all patients identified at increased risk of moderate MUPS in 2008 (n = 273), 13.5% (n = 37) developed a depressive and/or an anxiety disorder in 5 years follow-up, compared to 1.4% (n = 156) of the patients without MUPS, 12.3% (n = 56) of the patients identified at increased risk of mild MUPS and 19.6% (n = 12) of the patients with chronic MUPS (see Table 4).

Of the 11.419 patients, 337 patients (2.9%) were diagnosed with a confirmed medically diagnosis during follow-up (see Table 4). Of the patients within the moderate MUPS subgroup in 2008 (n = 273), 15.8% (n = 43) developed a medical explained diagnosis in the same ICPC chapter as the MUPS related symptoms in the index year, as compared to 2.1% (n = 231) of the patients without MUPS, 11.6% (n = 53) of the patients identified at increased risk of mild MUPS and 16.4% (n = 10) of the patients with chronic MUPS during 5 years follow- up. Of all patients who developed a medical diagnosis during follow-up, most diagnosis regarded in the ICPC chapter L (musculoskeletal). The risk for development of a medical diagnosis in patients within one of the MUPS subgroups is significantly higher compared with the non MUPS group.

Table 3 Prognostic accuracy for moderate MUPS patients after one and 5 years follow-up

non MUPS / maintained or deteriorated (2009)			non MUPS / maintained or deteriorated (2013)		
Positive Predictive value (95% CI)	Negative Predictive value (95% CI)	Odds ratio (95% CI)	Positive Predictive value (95% CI)	Negative Predictive value (95% CI)	Odds ratio (95% CI)
Moderate MUPS in 2008; n = 273					
0.670 (0.614–0.726)	0.825 (0.821–0.835)	9.82 (7.59–12.70)	0.487 (0.427–0.546)	0.778 (0.770–0.786)	3.33 (2.62–4.24)

Table 4 Depressive and/or anxiety disorder and medical diagnosis for patients in subgroups during 5 years follow-up

Depressive and/or an anxiety disorder during follow-up; n = 261						Medical explained diagnoses during follow-up; n = 337	
Anxiety disorder		Depressive disorder		Anxiety and depressive disorder			
% (n)	OR (95% CI)	% (n)	OR (95% CI)	% (n)	OR (95% CI)	% (n)	OR (95% CI)
Chronic MUPS in 2008; n= 61							
9.8 (6)	18.67 (7.72–45.15)[a]	8.1 (5)	11.01 (4.28–28.29)[a]	1.6 (1)	49.01 (5.38–446.41)	16.4 (10)	8.82 (4.42–17.60)[a]
Moderate MUPS in 2008; n = 273							
6.2 (17)	10.98 (6.33–19.05)[a]	6.9 (19)	8.68 (5.20–14.49)[a]	0.4 (1)	10.17 (1.13–91.38)	15.8 (43)	8.41 (5.92–11.95)[a]
Mild MUPS in 2008; n = 455							
4.4 (20)	7.64 (4.57–12.76)[a]	7.0 (32)	8.65 (5.70–13.12)[a]	0.9 (4)	24.07 (5.99–96.61)	11.6 (53)	5.93 (4.33–8.13)[a]
Non MUPS in 2008; n = 10.630							
0.0 (63)	–	0.9 (89)	–	0.0 (4)		2.1 (231)	–

[a]*There is a significant difference between the MUPS subgroups and non MUPS group on the development of a depressive and/or an anxiety disorder or a medical explained diagnosis, p < 0.05*

Discussion

The PRESUME screening demonstrated moderate prognostic accuracy for sustained MUPS related symptoms after 1 year and low to moderate accuracy after 5 years. Over a period of 5 years, more than 50% of the patients identified at increased risk of moderate MUPS had sustained MUPS related symptoms. Our findings indicate that the prognostic value of the PRESUME screening method is representative in patients with moderate MUPS without restrictions for the duration of complaints. The PRESUME method could support MUPS panel management in primary care, by combining early identification of moderate MUPS patients followed by a targeted intervention program to prevent chronicity.

The included study population is a representative sample of the Dutch population [37]. In the MUPS subgroups there is an overrepresentation of females, which is in line with other studies [10, 38]. Furthermore, the population in the JGPN database is also comparable to the Dutch population regarding urbanization and age [21].

Almost 20% of the patients with chronic MUPS and almost 15% of those identified at increased risk of moderate MUPS developed a depressive and/or an anxiety disorder in 5 year follow-up, which confirms a higher risk for mood disorders in patients with MUPS, as reported earlier [34, 39–41]. The percentage was lower compared to other studies [6, 34], which may be explained by the fact that patients with an existing diagnosis of a depressive and/or an anxiety disorder were excluded in step 2 of the PRESUME screening method. A disadvantage of excluding patients with a depressive and/or an anxiety disorder is that we also excluded MUPS patients with a mood disorder. However, according to the Dutch multidisciplinary guidelines this MUPS subgroup has specific treatment recommendations, which legitimates the exclusion in the PRESUME screening method [31, 32].

Of all patients within one of the MUPS subgroups in 2008, we hypothesized that less than 5% would develop a medical diagnosis during 5 years. Our results proved otherwise: 11.6% (n = 53) of the patients identified at increased risk of mild MUPS in 2008, 15.8% (n = 43) of those identified at increased risk of moderate MUPS and 16.4% (n = 10) of the patients with chronic MUPS was labelled with a medical diagnosis in the same ICPC chapter as in which they had MUPS in 2008, during the 5 years follow-up. In short, almost 50% of the patients identified at increased risk of MUPS will develop a medical diagnosis. However, this percentage is probably an overestimation since 54 of the 106 patients (50.9%) who were diagnosed with a medical diagnosis during follow-up, also still had MUPS related symptoms. Consequently, the MUPS related symptoms cannot

be explained by the medical diagnosis, and the medical diagnosis seems not always anatomically be related to the MUPS related symptoms. Nevertheless, patients identified at increased risk of moderate MUPS according to the PRESUME screening method might have an established medical diagnosis, since we only exclude patients with chronic obstructive pulmonary disease, hypertension or diabetes mellitus in the second step of the PRESUME screening method. Therefore, to ensure that we have identified patients in the right stage of MUPS, also due to the moderate prognostic accuracy, GPs should perform a validity check and filter out patients with an established medical diagnosis, to prevent that patients are incorrectly offered treatment for MUPS.

Our study has some strengths and limitations. A first strength is that we were able to analyze data from a large primary care cohort with routine care data, which makes our findings generalizable to other general practices in the Netherlands. Another strength is that this is the first study, as far as we know, that has focused on identifying and follow-up of patients identified at increased risk of moderate MUPS using electronic medical record data. Most studies so far focus on patients with chronic MUPS, while those identified at increased risk of moderate MUPS may be a better target for preventive interventions [18, 42, 43]. Besides the strengths, we also should note some limitations.

First, the PRESUME screening method is over inclusive since it is developed to identify patients at increased risk of having MUPS in the primary care patient population. Therefore, the selected ICPC codes of step 3 of the PRESUME screening method are diagnoses which have a higher risk of staying unexplained. As a consequence, the selection does lead to false positive and negative patients, and an additional check by the GP might be useful before inviting selected patients for a preventive intervention program. Second, there may be a possible underestimation of the number of patients that has developed chronic MUPS, since GPs are reluctant to diagnose a chronic MUPS syndrome in their strive to prevent further somatisation [44]. The low prevalence of chronic MUPS might also partly explain the low to moderate positive predictive value of our screening method in long term follow-up [45]. A third limitation is the possible variation in the data, since the data have been extracted from electronic files of participating practices and therefore depends on quality of GP registration. In the Netherlands, GPs have a specific guideline on adequate care registration with diagnosis patients using the ICPC as well as registration according to the "SOAP system" [27, 28]. Despite this guideline, the data may still be sensitive for registration errors. Therefore, our advice is to conduct a validity check by the GP, after patients are identified at increased risk of moderate MUPS according to the PRESUME screening method. A fourth limitation is the possibility of selection bias due to the eligibility criterion of having complete follow-up data, as well as the search for explanatory medical diagnosis in the same ICPC chapter

as the MUPS related diagnosis in 2008. In this way, we did miss patients who moved and switched GP during follow-up, and we may have missed diagnoses in other ICPC chapter that explained the original MUPS symptomatology. Furthermore, patients who were diagnosed with a depressive and/or an anxiety disorder, according to step two of the PRESUME screening method, were excluded and classified as non MUPS patients. This might also be a potential form of selection bias due to the known association between MUPS and an anxiety and/or depressive disorder [6, 34].

The prognostic accuracy for patients identified at increased risk of moderate MUPS according to the PRESUME screening method is moderate in early identification of patients with increased risk of moderate MUPS in primary care. An average of more than 50% of the patients who were identified with increased risk of moderate MUPS in 2008 are still consulting the GP at least five times a year with at least one MUPS related symptom during 5 years follow-up. This means that in a large proportion of patients identified with increased risk of moderate MUPS, the burden stays high with high consultation rate and impact on patients quality of life, as well as for GPs with challenging consultations, difficulties in identifying patients with MUPS, and doubts to pursue further diagnostic evaluation, leading to a deteriorating doctor-patient relationship [11, 12]. GPs found adequate management of MUPS challenging and they mainly focus on maintaining the doctor-patient relationship when patients keep presenting with MUPS [46]. Therefore, for both patients and GPs in primary care it is of interest to identify patients with increased risk of moderate MUPS.

The PRESUME screening method can support timely pattern recognition by the GP. After the identification of patients with moderate MUPS according to the PRESUME screening method, the GP can conduct a validity check and patients with an established medical diagnosis can be excluded as having an increased risk of moderate MUPS. Furthermore, the GP can exclude patients in which further diagnostic evaluation of the symptoms is needed. The identification of patients with moderate MUPS can support adequate management of patients with MUPS as well as the doctor-patient relation, since GPs can conduct a more comprehensive bio-psychosocial approach in their consultations [47]. In addition, the identification of patients with MUPS can support a more proactive panel management approach. Patients at risk can be actively approached by their GP, offering them a preventive intervention program. The intervention should focus on improving illness perception and self-management, contribute to a better recovery of the moderate MUPS symptoms and prevent chronic MUPS. Future research should focus on the development of this intervention and asses its effectiveness.

Conclusion

The prognostic accuracy of the PRESUME screening method using electronic medical record data for identification of moderate MUPS patients is moderate. However, it might be a useful method to identify patients at increased risk of moderate MUPS, if combined with a validity check by the GP.

Additional files

Additional file 1: 104 ICPC codes refer to MUPS related diagnoses

Abdomen
D01 Abdominal pain/ cramps general
D02 Abdominal pain epigastric
D04 Rectal/ anal pain
D06 Abdominal pain localized other
D08 Flatulence/ gas/ belching
D09 Nausea
D11 Diarrhoea
D12 Constipation
D18 Change faeces/ bowel movements
D93 Irritable bowel syndrome
T03 Loss of appetite
T08 Weight loss

Fatigue
A04 Weakness/tiredness general
.01 Chronic fatigue syndrome

Musculoskeletal
L01 Neck symptom/ complaint
L02 Back symptom/ complaint
L03 Low back symptom/ complaint
L05 Flank symptom/ complaint
L06 Axilla symptom/ complaint
L07 Jaw symptom/ complaint
L08 Shoulder symptom/ complaint
L09 Arm symptom/ complaint
L10 Elbow symptom/ complaint
L11 Wrist symptom/ complaint
L12 Hand/ finger symptom/ complaint
L13 Hip symptom/ complaint
L14 Leg/ thigh symptom/ complaint
L15 Knee symptom/ complaint
L16 Ankle symptom/ complaint
L17 Foot/ toe symptom/ complaint
L18 Muscle pain
.01 Fibromyalgia
L79 Sprain/ strain of joint NOS
.01 Whiplash trauma cervical spine

Cardiology-Respiratory
K01 Heart pain
K02 Pressure/ tightness of heart
K03 Cardiovasculair pain NOS
K04 Palpitations/ awareness of heart
K05 Irregular heartbeat other
K05 Irregular heartbeat other
L04 Chest symptom/ complaint

(Pseudo-)Neurology and ENT
A01 Pain gereral/ multiple sites
F13 Eye sensation abnormal
H02 Hearing complaint
H03 Tinnitus, ringing/buzzing ear
N01 Headache
N02 Tension headache
N03 Pain face
N05 Tingling fingers/feet/toes
N17 Vertigo/dizziness
.01 Sensation of unsteadiness
.02 Lightheadedness

Other
S01 Pruritis
R98 Hyperventilation syndrome

Psychiatry
A26 Fear of cancer NOS
A27 Fear of other disease NOS
B25 Fear of aids/ HIV
B26 Fear cancer blood/ lymph
B27 Fear blood/ lymph disease other
D26 Fear of cancer of digestive system
D27 Fear of digestive disease other
F27 Fear of eye disease
H27 Fear of ear disease
K24 Fear of heart disease
K25 Fear of hypertension
K27 Fear cardiovascular disease other
L26 Fear of cancer musculoskeletal
L27 Fear musculoskeletal disease other

N26 Fear cancer neurological system
N27 Fear of neurological disease other
P01 Feeling anxious/nervous/tense
P06 Sleep disturbance
P75 Somatization disorder
R26 Fear of cancer respiratory system
R27 Fear of respiratory disease other
S26 Fear of cancer of skin
S27 Fear of skin disease other
T26 Fear of cancer of endocrine system
T27 Fear endocrine/metabolic dis other
U26 Fear of cancer of urinary system
U27 Fear of urinary disease other
X23 Fear sexually transmitted disease (f)
X24 Fear of sexual dysfunction female
X25 Fear of genital cancer female
X26 Fear of breast cancer female
Y24 Fear of sexual dysfunction male
Y25 Fear sexually transmitted disease (m)
Y26 Fear of genital cancer male
Y27 Fear of genital disease male other
Z29.01 Burnout / stress

Urological/ Genital complaints
U02 Urinary frequency/urgency
U05 Urination problems other
X01 Genital pain female
X02 Menstrual pain
X03 Intermenstrual pain
X04 Painful intercourse female
X09 Premenstrual symptom/complaint
X11 Menopausal symptom/complaint
X15 Vaginal symptom/complaint other
X16 Vulval symptom/complaint
X17 Pelvis symptom/complaint female
Y01 Pain in penis
Y02 Pain in testis/scrotum
Y04 Penis symptom/complaint other
Y08 Sexual function symptom/ complaint (m)

Additional file 2: Medically explained diagnoses

Chapter A

A70 Tuberculosis
A75 Infectious mononucleosis
A77 Viral disease other/NOS
A78.05 Lyme disease, Lyme borreliosis
A79 Malignancy NOS
A86 Toxic effect non-medicinal substance
A91.06 subclinical hypothyroidism
A91.07 subclinical hyperthyroidism

Chapter B

B72 Hodgkin's disease/lymphoma
B72.01 Hodgkin's disease
B72.02 Non-Hodgkin lymphoma
B73 Leukemia
B74 Malignant neoplasm blood other
B74.01 Multiple myeloma
B77 Injury blood/lymph/spleen other
B78 Hereditary haemolytic anaemia
B78.01 thalassaemia
B78.02 sickle-cell anaemia
B78.03 Anemia G6PD deficiency
B79 Congenital anomaly blood/lymph other
B80 Iron deficiency anaemia
B81 Anaemia, Vitamin B12/folate def
B81.01 folate deficiency
B81.02 Anaemia vit B12
B82 Anaemia other/unspecified
B90 HIV-infection/AIDS
B90.02 AIDS/ARC

Chapter D

D72.03 Acute hepatitis C
D72.05 Carrier hepatitis C / chronic hepatitis C
D74 Malignant neoplasm stomach
D75 Malignant neoplasm colon/rectum
D76 Malignant neoplasm pancreas
D77 Malig. neoplasm digest other/NOS
D77.01 Malignant esophagus
D77.02 Malignant salivary glands
D77.03 Malignant lip / mouth / tongue
D77.04 Malignant liver / gallbladder / biliary
D84.03 oesophagial reflux with oesophagitis
D86 Peptic ulcer other
D86.01 Ulcus ventriculi
D94 Chronic enteritis/ulcerative colitis
D94.01 Ulcerative colitis
D94.02 Crohn's disease
D99.06 Celiac Disease

Chapter F

F74 Neoplasm of eye/adnexa
F74.01 Malignant eye/adnexa

Chapter H

H75 Neoplasm of ear
H75.01 Malignant ear

Chapter K

K72 Neoplasm cardiovascular
K72.01 Malignant cardiovascular
K74 Ischaemic heart disease w. angina
K74.01 Unstable angina
K74.02 Stable angina
K75 Acute myocardial infarction
T73 Neoplasm endocrine oth/unspecified
K77 Decompensatio cordis
K77.01 Acuut decompensatio cordis/astma cardiale
K77.02 Chronic decompensatio cordis
K78 Atrial fibrillation/flutter
K79 Paroxysmal tachycardia
K79.01 supraventricular tachycardia
K79.02 ventricular tachycardia
K80 Cardiac arrhythmia NOS
K80.01 supraventricular extrasystoles
K80.02 ventricular extrasystoles
K80.03 Sick sinus syndrome

Chapter L

L70 Infection of musculoskeletal system
L70.01 osteomyelitis
L70.02 septic arthritis
L71 neoplasm musculoskeletal
L71.01 Malignant neoplasm musculoskeletal
L76.06 Fracture spine
L76.07 Fracture pelvis

L83.01 herniated cervical
L84 Osteoarthritis / spine spondylosis
L86.01 HNP (thoracic / lumbar)
L88 Rheumatoid/seropositive arthritis
L88.01 Rheumatoid arthritis
L88.02 Morbus Bechterew (ankylosing spondylitis)
L89 Osteoarthrosis of hip
L90 Osteoarthrosis of knee
L99.06 Tietze Syndrome
L99.12 Polymyalgia rheumatica

Chapter N

N74 Malignant neoplasm nervous system
N75 Benign neoplasm nervous system
N76 Neoplasm nervous system unspec.
N86 Multiple sclerosis
N87 Parkinsonism
N87.01 Parkinson's disease
N91 Facial paralysis/bell's palsy
N92 Trigeminal neuralgia
N94.01 Guillain-Barré syndrome
N99.01 ALS
N99.02 Myasthenia gravis
N99.03 Muscular dystrophy

Chapter P

Not applicable

Chapter R

R83.02 Sarcoïdosis
R84 Malignant neoplasm bronchus/lung
R85 Malignant neoplasm respiratory, other
R95 Chronic obstructive pulmonary disease
R96 Astma
R96.01 reactive airways disease

Chapter S

S77 Malignant neoplasm of skin
S77.01 basal cell carcinoma
S77.02 squamous cell / squamous cell carcinoma
S77.03 Malignant melanoma
S77.04 Kaposi's sarcoma

Chapter T

T71 Malignant neoplasm thyroid
T72 Benign neoplasm thyroid
T85 Hyperthyroidism/thyrotoxicosis
T86 Hypothyroidism/myxoedema
T90.01 juvenile onset diabetes; type 1 diabetes
T90.02 late onset diabetes; type 2 diabetes
T99.08 Cushing's syndrome
T99.09 Addison's syndrome

Chapter U

U75 Malignant neoplasm of kidney
U76 Malignant neoplasm of bladder
U77 Malignant neoplasm urinary other
U79 Neoplasm urinary tract NOS

Chapter W

Not applicable

Chapter X

X75 Malignant neoplasm cervix
X76 Malignant neoplasm breast female
X76.01 Adenocarcinoma mom female
X77 Malignant neoplasm genital other (f)
X77.01 Endometrial cancer
X77.02 Malignant ovary

Chapter Y

Y77 Malignant neoplasm prostate
Y78 Malignant neoplasm male genital other
Y78.01 Malignant penis
Y78.02 Malignant testis
Y78.03 Malignant breast

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Chapter 3

Identification of treatment modalities based on expert opinions

Based on:
Identifying Treatment Modalities for a Multidisciplinary and Blended Care Intervention for Patients With Moderate Medically Unexplained Physical Symptoms: Qualitative Study Among Professionals

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Paula E. van Westrienen
Martijn F. Pisters
Marloes Gerrits
Cindy Veenhof
Niek J. de Wit

Abstract

Background

Medically unexplained physical symptoms (MUPS) are a substantial health problem in primary care with a high burden for patients, general practitioners, and the health care system. Most studies focus on chronic MUPS patients. Little research is conducted in patients with moderate MUPS, and an effective primary care intervention for prevention of chronic MUPS is lacking.

Objective

The objective of our study was to identify treatment modalities based on expert opinions for the development of a multidisciplinary and blended intervention for patients with moderate MUPS to prevent chronicity.

Methods

Two focus groups with 8 and 6 experts (general practitioners, physical therapists, psychologists, and mental health nurses) were carried out. The focus groups were structured using the nominal group technique.

Results

A total of 70 ideas were generated from two nominal group meetings, and 37 of these got votes, were included in the rank order, and were sorted into 8 separate themes. According to the participants, the most important treatment modalities for a multidisciplinary and blended intervention in patients with moderate MUPS were (1) coaching to a healthier lifestyle, (2) education regarding psychosocial factors, (3) therapeutic neuroscience education, (4) multidisciplinary intake, (5) multidisciplinary cooperation and coordination, (6) relaxation or body awareness exercises, (7) clear communication by professionals to the patient, and (8) graded activity. Five independent researchers checked the ideas and linked them to themes to confirm the content analysis and check the validity of the themes.

Conclusions

From professional expert perspectives, 8 themes should be included in a multidisciplinary and blended intervention to prevent chronicity. These themes provide a first step in developing an intervention for patients with moderate MUPS. Future research should focus on further development steps in which patients with moderate MUPS should be involved to determine if the intervention matches their needs.

Introduction

Medically unexplained physical symptoms (MUPS) are physical complaints (eg, pain, fatigue, dizziness) that last for at least a few weeks and cannot be explained by a medical condition after adequate medical examination [1,2]. Approximately 20% of patients with MUPS still experience unexplained physical symptoms after 3 months, and a third of patients presenting with MUPS maintain unexplained symptoms after 5 years [3]. Symptoms can be categorized into moderate MUPS and chronic MUPS [2,4]. Moderate MUPS symptomatology can be of any type and intensity in 2 or 3 domains (eg, musculoskeletal, fatigue, cardiology-respiratory) with psychological and physical distress. Chronic MUPS symptomatology is within more domains with psychological and physical dysfunction (eg, fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome) [2,4]. The estimated prevalence of moderate MUPS is 15%, and chronic MUPS occurs in approximately 2.5% of patients in primary care [4-6]. The burden (eg, physical, social, emotional) of MUPS is high based on the decrease in quality of life and increase in health care use for patients [7-9]. Furthermore, the burden is high for general practitioners and society since general practitioners do not recognize patients with MUPS early, and they experience difficulties in treating and managing patients with MUPS [10-12], leading to increased direct health care costs and indirect costs (eg, work- and insurance-related costs) [9].

Many studies have already been conducted in patients with chronic MUPS to assess the efficacy of psychological, pharmacological, exercise therapy, or combined treatment approaches [13-18]. So far, systematic reviews based on low-quality evidence suggest that cognitive behavioral therapy might be an effective psychological treatment [17,18]. The focus of pharmacological interventions should be on action of the central nervous system (eg, antidepressants) instead of restoration of peripheral physiological dysfunction (eg, nonsteroidal anti-inflammatory drugs) [16]. Furthermore, compelling evidence for neuroscience education is found on pain, disability, catastrophization, and physical performance [13]. In a session on neuroscience education, the patient is educated on the neurobiology and neurophysiology of pain and pain processing by the nervous system [13]. Systematic reviews based on low- to moderate-quality evidence suggest that exercise therapy has a positive effect on physical function [14,15]. Despite the evidence for the more isolated interventions, it is suggested that treatments should be multimodal in patients with MUPS, with components of exercise, education, and integrating aspects of a psychological approach [13,16,17].

For the development of multimodal interventions, expert opinions and patient needs should be taken into account [19]. Different studies have already focused on the

management of MUPS. In a qualitative analysis on expert opinions, some relevant elements were identified for successful management of MUPS: creating a safe therapeutic environment and using generic (eg, motivational interviewing) and specific (eg, cognitive approaches) interventions [20]. Furthermore, earlier research has indicated that explanation of the symptoms is an important management strategy in patients with MUPS [21,22].

Many qualitative and quantitative studies have focused on patients with chronic MUPS [13-18,21,23-26]. Little research has been conducted in patients with moderate MUPS, but preventing chronicity in moderate MUPS to decrease the burden for patients, general practitioners, and society is important [27]. Recently, we developed a screening method (PRESUME: preventive screening of medically unexplained physical symptoms) to identify patients with moderate MUPS using the electronic medical records of the general practitioner. The method consists of 3 steps based on consultation frequency, exclusion of medical and/or psychiatric diagnosis, and identification of chronic MUPS and moderate MUPS. Patients are identified with chronic MUPS when they are diagnosed with a functional somatic syndrome (eg, fibromyalgia, chronic fatigue syndrome, or irritable bowel syndrome), and patients with moderate MUPS have MUPS-related symptoms without a MUPS diagnosis. Despite its limited prognostic accuracy, the PRESUME screening method facilitates identification of patients with moderate MUPS. In the next step we aim to develop an effective multidisciplinary and blended primary care intervention to prevent chronicity in patients with moderate MUPS. The expectation is that the integration of face-to-face sessions with eHealth modules, called blended care, will promote self-management. Furthermore, a blended care intervention may lead to a decrease of costs since the face-to-face sessions are not performed on a weekly basis. Blended care has already been proven effective in other studies [28,29]. The intervention will be performed in primary care; therefore, a physical therapist and mental health nurse should be involved in the intervention since both disciplines treat patients with MUPS in primary care in the Netherlands [2]. For development of the intervention, the Medical Research Council (MRC) framework will be used. The MRC framework include several phases: development, feasibility and piloting, evaluation, and implementation [19]. In this study we focused on identifying existing relevant themes for the intervention as a first part of the development phase of the MRC framework. Professionals involved in the clinical management of MUPS were asked to participate. The aim of this study was to identify expert-based treatment modalities for a multidisciplinary intervention for patients with moderate MUPS in primary care.

Methods

Design

A qualitative study using focus groups according to the nominal group technique (NGT) was performed [30]. Preconditions were that the intervention will be multidisciplinary and blended, with the focus on self-management.

Participants

Professionals involved in the clinical management of patients with MUPS were approached to participate in the study. Eligible participants were selected through purposive sampling and finally included based on availability. Purposive sampling was applied to obtain variation in disciplines (general practitioner, psychosomatic physical therapists, health care psychologists, and mental health nurses). The number of participants in a nominal group meeting was based on the recommendation of a maximum of 9 or 10 participants per group [31]. Based on the involvement of different disciplines, multiple nominal group meetings were organized [32]. We started with organizing 2 nominal group meetings, so the participants were divided into 2 groups. If there were no agreement between the items mentioned in the first 2 meetings, extra meetings with other participants would be organized until data saturation was achieved. The study was carried out according to Dutch privacy legislation rules. Written informed consent was obtained from all participants before the start of the focus group. In the first focus group, one general practitioner, one physical therapist, 2 psychosomatic physical therapists, 2 health care psychologists, and 2 mental health nurses participated. In the second focus group, 2 general practitioners, one physical therapist, 2 psychosomatic physical therapists, and one psychologist/physical therapist participated. Since the results of the second group discussions did not add major new ideas compared to the ideas identified in the first group, saturation was assumed and no additional group sessions were held.

Participants had a median work experience of 18 years (interquartile range [IQR] 20), where 21% (3/14) had less than 10 years of work experience, 29% (4/14) had 10 to 20 years of working experience, and 50% (7/14) had 20 years or more of work experience. In addition, participants had a median experience of treating patients with MUPS of 9 years (IQR 18), where 50% (7/14) had less than 10 years of experience in treating patients with MUPS, 21% (3/14) had 10 to 20 years of experience in treating patients with MUPS, and 29% (4/14) had 20 years or more experience in treating patients with MUPS. Some participants had other work activities besides their profession such as a researcher, teacher, or public administrator. Demographic characteristics of the participants are shown in Table 1.

Table 1. Demographic characteristics of the participants (n=14).

Characteristics	Values
Profession, n (%)	
General practitioner	3 (21)
Physical therapist	2 (14)
Psychosomatic physical therapist	4 (29)
Psychologist/physical therapist	1 (7)
Health care psychologist	2 (14)
Mental health nurse	2 (14)
Female, n (%)	9 (64,3%)
Age in years, median (IQR[a])	46.5 (20)
Years of general work experience, median (IQR)	18 (20)
Years of experience treating patients with MUPS[b], median (IQR)	9 (18)
Other work activities[c], n (%)	
Research-assistant	1 (7)
Junior researcher	1 (7)
Postdoc researcher	1 (7)
Senior researcher	1 (7)
Clinical health scientist	1 (7)
Clinical epidemiologist	1 (7)
Teacher	5 (36)
General practitioner, special interest musculoskeletal	1 (7)
General practitioner, special interest mental health care	1 (7)
Public administrator	1 (7)

[a] *IQR: interquartile range.*
[b] *MUPS: medically unexplained physical symptoms.*
[c] *Some participants are classified in multiple categories.*

Procedure

NGT is a formal stepwise consensus procedure that uses structured interaction within the group. Ideas were generated focusing on optimization of moderate MUPS management [30]. NGT is a structured group meeting, which is of interest in a heterogenic group of participants [33]. This technique enables participants to gather individual ideas, obtain ideas from other members, and rank ideas with equal input from all participants.

- Introduction of the nominal question: welcome and introduction of NGT and the nominal question.
- Silent generation of ideas: participants are asked to write down their individual list of ideas that come to mind regarding the nominal question without discussing with or consulting others.
- Presenting of ideas: sheets with individual ideas are gathered, and each participant presents their ideas to the group without discussion.
- Group discussion: all ideas are evaluated, clarified, and discussed one by one. Ideas can be specified when necessary. Similar items can be merged but only after agreement of all participants.
- Voting and ranking of ideas: participants are asked to individually rank the 5 most important items without discussion with other group members. Scores are summed (an item receives 5 points for a number 1 position, 4 points for a number 2 position, etc), and a final rank order is presented.

A week before the meeting, participants received information about the meeting, and the research question was introduced by the principal researcher: "Which treatment modalities should be part of the multidisciplinary treatment program for moderate MUPS to prevent chronic MUPS?" At the beginning of the meeting, participants were introduced and the role of the facilitator (assistant; presents all ideas and rankings in PowerPoint) and principal researcher (moderator of the discussion) were explained. In addition, the purpose and procedure of the meeting were explained, the research question was displayed, and the definition of moderate MUPS was specified (patients who have had at least 5 general practice consultations during the past 12 months of which at least 3 were based on the presence of MUPS-related symptoms; furthermore, patients should have psychological and physical distress). Subsequently, the 4 structured steps according to the NGT procedure were explained and followed [30].

The first step is silent generation, where all participants wrote down ideas around the question individually and privately for approximately 20 minutes. The second step was a round-robin format, where all participants shared their ideas one by one with

the group. One participant at the time stated a single idea, which was presented on a screen in front of the group by the facilitator. This process was continued until all ideas from participants were listed and displayed on the screen. There was no discussion at this stage. In the third step, all collected ideas were clarified and discussed in the group. Similar ideas were grouped together but only after agreement by all participants. Discussion ended when no new ideas were generated or grouped together and data saturation within the group was thus achieved. In the fourth step, participants were able to independently rank 5 ideas from all generated ideas. In this ranking process, participants gave 5 votes to the most important idea and the fifth most important idea got one vote. After the 4 steps, the facilitator collected the voting sheets, and the scores for each idea were presented. The group meeting was audiotaped to verify data and use the information for ongoing analysis after the meeting.

Data Analysis

NGT enables participants to be involved in data analysis by composing a rank order. Rank orders of the 2 groups were merged into one final rank order using a structured method for analyzing multiple group data [34]. All ideas were listed in the final rank order to combine ideas into themes by the principal researcher (content analysis). Subsequently, each theme got a definition. To confirm the content analysis as well as increase the reliability, 5 independent researchers who were not involved in the study checked the ideas and decided to which theme they belonged to determine if themes should be more clearly defined or maybe combined or redivided [34]. In the last step, all themes were ranked according to the number of ideas that formed the theme, the number of times the ideas were ranked in the top 5, and the relative score of the ideas within the group rankings. Only the ideas that had received votes were included in the rank order. Multigroup data analysis procedure [34] is as follows:

- Capture data on computer: sets of items with the individual and group scores for each item can be entered on a spreadsheet.
- Identifying the overall top 5 per group: sets of items were ordered according to the importance of the items as scored by each group. Subsequently, the top 5 of the most important items of each group are identified as described by the steps of van Breda et al [34].
- Content analysis of the data: the principal investigator (PEvW) will combine the items from all groups into groups of items. This process is repeated a few times, and themes are created. An item can fall into one theme only. Subsequently, a definition to each theme is created. This is a time-consuming process.
- Confirm the content analysis: the content analysis is peer-reviewed by inde-pendent researchers who have not been involved in the NGT research process.

Subsequently, the principal investigator determines whether themes should be more clearly defined or maybe combined or redivided.

- Calculating combined ranks: the relative importance of each theme to all the groups combined is calculated. The final rank provides a consolidation of all items generated and ranked by the participants.

Results

From the 2 nominal group meetings, 70 ideas were generated (37 in group 1 and 33 in group 2), of which 37 received scores from the participants (19 in group 1 and 18 in group 2). All ideas from both focus groups were ordered according to the scores of the participants. Subsequently, the top 5 ideas were identified. The idea with the highest score in both focus groups was "education about the complaints of the patient." Both focus groups indicated that it should be at the start of an intervention.

Participants of the first focus group scored as the second most important idea "education about factors which affect the complaints, to make the connection with possible perpetuating factors." The third most important idea was the "treatment demand." The participants found it important that the treatment demand should be clear at the end of the intake for a tailored intervention. The fourth most important idea was that professionals should pay attention to patients' lifestyle, where self-management in general daily life of patients is of interest. The fifth most important idea of the first focus group was that "patients should get more insight in their emotions, behavior, and thoughts in relation with the complaints." In the second focus group, the participants scored as second most important idea "interdisciplinary collaboration." The third most important idea was "the patient should have problem-solving skills." Participants expected that patients with problem-solving skills would recognize challenges as well as develop self-management strategies. Fourth, "cognitive behavioral interventions are of interest to help patients managing their problems." The participants found it important that patients learn to make the connection between their thoughts, feelings, and behavior and their complaints with cognitive behavioral interventions. Finally, participants in the second focus group mentioned "education and coaching on lifestyle" as the fifth most important idea.

After the identification of ideas and their ranking in both focus groups, the ranked ideas were merged into one final rank order according to the structured method for analyzing multiple group data [34]. This final rank order was analyzed, and all ideas were divided into themes by the principal researcher (Multimedia Appendix 1). Eight separate themes with definitions were composed by the principal researcher.

1. Coaching to a healthier lifestyle: coaching to a healthier lifestyle and behavioral changes through self-management as well as a balance between burden and capacity with attention to coping strategies
2. Education regarding psychosocial factors: education on possible precipitating and maintaining factors of the complaints with the connection between thoughts, emotions, and behavior
3. Therapeutic neuroscience education: education of central sensitization
4. Multidisciplinary intake: a multidisciplinary intake with both physical aspects (eg, by the physical therapist) and mental aspects (eg, by a mental health nurse). During the intake, both disciplines should focus on the complaints (also checking if the patient has doubts about having a medical diagnosis), cognitions, emotions, behavior, and social environment of the patients, but from a different perspective. Additionally, the treatment demand and goals of the patient should be clear before the actual start of the intervention
5. Multidisciplinary cooperation and coordination: multidisciplinary cooperation between, for example, the general practitioner, physical therapist, and mental health nurse with established consultation meetings where the general practitioner will have the coordinating role during the intervention
6. Relaxation or body awareness exercises: relaxation or body awareness exercises should be part of the intervention (eg, general relaxation techniques [progressive relaxation or autogenic training], mindfulness, and exercises according to psychomotor therapy)
7. Clear communication of professionals to the patient: professionals should express themselves in the same way toward the patient during education sessions and should have insight into their own cognitions about MUPS
8. Graded activity: gradually increasing the amount of physical activity in a time-contingent way based on individual goal setting, using preset quotas and principles of operant conditioning

The composed themes were validated by 5 independent researchers who were not involved in the study. They checked the ideas and decided in which theme they belong. This led to the adjustment of 7 ideas into other themes and a more clear definition of 3 themes. After validating our composed themes, the relative importance of each theme was determined according to a ranking score. "Coaching to a healthier lifestyle" had the highest ranking score and was the first theme. "Graded activity" had the lowest ranking score. This ranking score indicated which parts of the multidisciplinary and blended primary care intervention were most important from a professional expert perspective.

Discussion

Principal Findings

The aim of this study was to determine treatment modalities according to professional experts for the development of a multidisciplinary and blended primary care intervention in patients with moderate MUPS to prevent chronic MUPS. According to the ideas and their ranking, 8 themes were important. Our study is the first qualitative study focusing on patients with moderate MUPS, since earlier research focused on patients with chronic MUPS [20,21]. Additionally, qualitative studies on MUPS and health care professionals included general practitioners only. As far as we know this is the first qualitative study in which all health care professionals involved in management of MUPS in primary care were included.

Although comparison with results of earlier research is difficult since it focused on management of chronic MUPS, some of the themes we created in our study were also proven effective in patients with chronic MUPS [2,13,35,36]. The Dutch Multidisciplinary Guideline for MUPS and Somatoform Disorders advises to start the intake by exploring the somatic, cognitive, emotional, behavioral, and social dimensions of the complaints [2], which is in line with the results of the nominal group meetings. Evidence for neuroscience education is found for patients with chronic musculoskeletal pain disorders [13]. Furthermore, progressive muscle relaxation as a relaxation exercise is effective on intensity and number of symptoms, quality of life, and comorbid symptoms for patients with multiple somatoform symptoms [36], and graded activity had a medium effect for patients with chronic fatigue syndrome on fatigue severity reduction [35]. These similarities could possibly be due to the fact that professional experts might know the effective interventions for patients with chronic MUPS and found them also applicable for patients with moderate MUPS.

It can also be related to the clinical presentation, as both patients with moderate MUPS and patients with chronic MUPS experience physical and psychological problems [4]. Although the themes partly overlap with the key management aspects of chronic MUPS, none of the intervention studies on patients with chronic MUPS integrated all aspects in a multidisciplinary and blended primary care intervention.

Strengths and Limitations

This study has a few strengths. First, a group of experts with representatives in all relevant disciplines was included. Therefore, an answer as broad as possible to our question was gathered. Second is the choice of the nominal group technique. Since the intervention for patients with moderate MUPS will be multidisciplinary, we provided a qualitative

study with a heterogenic group of professional experts. The structure of the NGT enables group discussion and assures equal input from all participants instead of the possibility that only one participant is mostly speaking [37]. A third strength is that we checked our content analysis by letting independent researchers who were not previously involved in the study check the ideas and decide in which theme they belong [34]. This step in the data analysis of the study is to test the content validity of our themes and enhances the interrater reliability. Besides the strengths, some limitations should be noted. Firstly, a limitation of the purposive sampling strategy is the nonrandom selection of participants. However, with this nonrandom selection of participants, a representative group of all relevant disciplines involved in the clinical management of patients with MUPS was gathered. Furthermore, all participants were aware of the last scientific findings in MUPS research. If a random selection of participants were conducted, the possibility existed that not all relevant disciplines would be selected. Second, some participants seemed to have difficulties with the focus on patients with moderate MUPS as a target group and therefore mentioned ideas that had probably more focus on chronic MUPS. At the beginning of the meeting, the principal researcher pointed out the definition of moderate MUPS and specified to mention ideas that focused on treatment modalities for patients with moderate MUPS. The participants got the definition of moderate MUPS on paper. During the discussion step of the NGT, participants addressed to each other that some ideas might better fit as treatment modalities for patients with chronic MUPS. This led to the removal of some ideas by participants but only after agreement of all participants. In this way, ideas with the focus on treatment modalities for patients with moderate MUPS remained and could get ranked during the last step of the NGT procedure. A third limitation is that generalizability to foreign countries might be complex due to the differences with respect to the health care systems of other countries. Despite these differences, our identified themes for an intervention can be applied in other health care systems or countries since the context for an intervention will not differ.

The results of this study are the basis for the development of a multidisciplinary and blended primary care–focused intervention for patients with moderate MUPS to prevent chronicity. A new primary care intervention would be of great value in clinical practice. In the next step, principles of the Center for eHealth Research road map can be used to focus on the integration of face-to-face sessions using the eHealth modules [38].

Conclusion

From professional expert perspectives, 8 themes should be included in a multidisciplinary and blended intervention to prevent chronicity. These themes provide a first step in developing an intervention for patients with moderate MUPS. Future research should focus on further development steps of the MRC framework in which patients with moderate MUPS should be involved to determine if the intervention matches their needs.

Multimedia Appendix 1

All ideas from both focus groups divided into eight themes.

Themes	Items focus group 1	Items focus group 2
Coaching to a healthier lifestyle	• Coaching on lifestyle • Balance between performance and capacity • Adjustment of the coping style • Communication coaching techniques (motivational interviewing, problem solving)	• Acceptance and commitment therapy • Provocative psychology • The patient should develop problem-solving skills • Coaching towards a dailyschedule • Lifestyle education and coaching • Involvement of relatives in the intervention
Education regarding perpetuating factors	• Psycho-education about perpetuating factors • Insight in persisting complaints with the connection between thoughts, emotions and behaviour • Insight in the link between the complaints and the family system	• Cognitive behavioural interventions
Therapeutic neuroscience education	• Psycho-education about MUPS	• Education about MUPS with reference to an explanatory model
Multidisciplinary intake	• Treatment demand • Identifying complaints according to the SCEGS (somatic, cognitive, emotional, behavioural and social factors) • Checking reassurance regarding the absence of a medical diagnosis • Symptom registration in a patient diary	• Identifying illness beliefs • Monitoring physical behaviour • Creating and evaluating an action plan
Multidisciplinary cooperation and coordination	• Regular multidisciplinary consultations	• Interdisciplinary collaboration
Relaxation / body awareness exercises	• Body awareness • Relaxation exercises • Coping with anxiety/stress • Emotion regulation through movement	• Relaxation techniques • Body awareness exercises • Psychomotor interventions
Clear communication of professionals to the patient	• Clear referral of the general practitioner	• Training of the professional (communication techniques) • Training of the professionals according to their cognitions about MUPS
Graded activity	• Graded activity	• Time contingent approach

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Chapter 4

Effectiveness of the PARASOL intervention - study protocol

Based on:
Effectiveness of a blended and integrated mental health and physical therapy intervention program (PARASOL) for patients with moderate medically unexplained physical symptoms to prevent chronicity: study protocol of a cluster randomized clinical trial

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Paula E. van Westrienen
Martijn F. Pisters
Suze A.J. Toonders
Marloes Gerrits
Cindy Veenhof
Niek J. de Wit

Abstract

Background

Medically unexplained physical symptoms are an important health problem in primary care, with a spectrum from mild to chronic. The burden of chronic medically unexplained physical symptoms is substantial for patients, health care professionals, and society. Therefore, early identification of patients with moderate medically unexplained physical symptoms is needed in order to prevent chronicity. The preventive screening of medically unexplained physical symptoms (PRESUME) screening method was developed using data from the electronic medical record of the patients' general practitioner and demonstrated its prognostic accuracy to identify patients with moderate medically unexplained physical symptoms. In the next step, we developed a proactive blended and integrated mental health and physical therapy intervention program (PARASOL) to reduce complaints of moderate medically unexplained physical symptoms, stimulate self-management, and prevent chronicity.

Objective

The primary objective of this study is to investigate the effectiveness of the blended PARASOL intervention on the impact of symptoms and quality of life in patients with moderate medically unexplained physical symptoms compared with usual care. Secondary objectives are to study the effect on severity of physical and psychosocial symptoms, general health, physical behavior, illness perception, and self-efficacy in patients with moderate medically unexplained physical symptoms as well as to determine the cost-effectiveness of the program.

Methods

This paper presents the study protocol of a multicenter cluster randomized clinical trial. Adult patients with moderate medically unexplained physical symptoms will be identified from electronic medical record data using the PRESUME screening method and proactively recruited for participation in the study. Cluster randomization will be performed at the level of the participating health care centers. In total 248 patients with moderate medically unexplained physical symptoms (124 patients per arm) are needed. The PARASOL intervention is a 12-week blended primary care program consisting of 4 face-to-face consultations with the mental health nurse and 5 physical therapy sessions, supplemented with a Web-based program. The Web-based program contains (1) information modules and videos on self-management and educative themes, (2) videos and instructions on prescribed home exercises, and (3) assignments to gradually increase the physical activity. The program is directed at patients' perception of symptoms as well as modifiable prognostic risk factors for chronicity using therapeutic

neuroscience education. It encourages self-management, as well as an active lifestyle using a cognitive behavioral approach and graded activity. Primary outcomes are impact of symptoms and quality of life. Secondary outcomes are severity of physical and psychosocial symptoms, general health, physical behavior, illness perceptions, self-efficacy, and cost-effectiveness. All measurements will be performed at baseline, 3 and 12 months after baseline. Retrospective cost questionnaires will also be sent at 6 and 9 months after baseline and these will be used for the cost-effectiveness analysis.

Results

The intervention has been developed, and the physical therapists and mental health nurses in the participating experimental health care centers have received two days of training on the content of the blended PARASOL intervention. The recruitment of health care centers started in June 2016 and inclusion of patients began in March 2017. Follow-up assessments of patients are expected to be completed in March 2019.

Conclusions

This study is the first randomized clinical trial to determine the effectiveness (including cost-effectiveness) of a proactive, blended, and integrated mental health and physical therapy care program for patients with moderate medically unexplained physical symptoms. The findings will help to improve the treatment for patients with moderate medically unexplained physical symptoms and prevent chronicity.

Trial Registration

Netherlands Trial Register NTR6755; http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=6755 (Archived by WebCite at http://www.webcitation.org/6ywporY7u).

Introduction

Medically unexplained physical symptoms (MUPS), especially pain, dizziness, and fatigue are frequent in primary care, in fact 25%-50% of all symptoms presented during consultations cannot be adequately medically explained [1]. If there are physical complaints for which no medical condition can be found after adequate medical examination, they will be defined as MUPS [2,3].

MUPS can be regarded as a spectrum ranging from mild unexplained physical symptoms (low incidence, one or two domains, low impact), to moderate symptoms (more frequent, two or three domains, higher impact) and finally to persisting or chronic MUPS (high impact, more clusters involved, chronic; eg, fibromyalgia, chronic fatigue syndrome, or irritable bowel syndrome) [3,4]. In this spectrum, mild MUPS have an estimated prevalence of 70% to 80% [4,5]. These patients consult their general practitioner (GP) for a symptom that cannot be explained immediately, but the symptoms improve within 2 weeks [6]. Moderate MUPS have an estimated prevalence of approximately 15%, where patients still experience unexplained symptoms after three months without a diagnosis of a functional somatic syndrome [6]. Patients with chronic MUPS will have a symptom duration of at least six months, with the presence of a functional somatic syndrome, such as fibromyalgia, chronic fatigue syndrome or irritable bowel syndrome, or a somatic symptom disorder according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition [4,6,7]. Patients with chronic MUPS occur in approximately 2.5% in primary care, and 3% of the GP consultations are MUPS consultations [1,8].

Despite the low prevalence of chronic MUPS, the burden is substantial [1], with a high impact on patients' quality of life and daily functioning. Compared with the general population, as well with other patient groups such as major depressive disorder and cancer patients, patients with chronic MUPS report a lower quality of life [9,10]. Moreover, patients with MUPS consult a GP more frequently, but GPs find adequate management of MUPS challenging [11]. GPs frequently focus on exclusion of a somatic disease by recommending somatic interventions such as drug prescriptions, an investigation or a referral to a specialist; while patients often do not request for somatic interventions [12]. Furthermore, GPs face difficulty in the timely recognition of patients with MUPS [13]. On average, it takes two years to obtain a diagnosis. During this time period patients have on average 15 GP consultations, 8 visits to a hospital specialist and 14 sessions with the physical therapist [10]. Almost 40% of patients with MUPS report absenteeism from work [10]. As a result, MUPS are associated with increased direct and indirect costs related to health care expenditure as well as work and insurance related costs [10,14].

Much research has been conducted on effective interventions for chronic MUPS. Neurosciences-based therapeutic education, cognitive behavioral therapy, and exercise therapy have been shown to be effective treatment modalities in patients with MUPS [15-18]. Overall, the vast majority of these studies included patients with chronic MUPS. So far little research has been conducted in patients with moderate MUPS, partly due to the fact that adequate methods for early identification are lacking. Early identification of patients with moderate MUPS would enable interventions directed at prevention of chronicity, which ultimately might decrease the burden of these symptoms for patients, health care professionals and society.

Recently, a screening method (PRESUME; preventive screening of medically unexplained physical symptoms) has been developed to identify patients with moderate MUPS using data from the electronic medical record of the patient's GP as shown in Figure 1 [19]. The PRESUME screening method showed acceptable prognostic accuracy over a five-year follow-up [19]. For patients with moderate MUPS, we developed a proactive, blended, and integrated mental health and physical therapy care program to prevent chronicity.

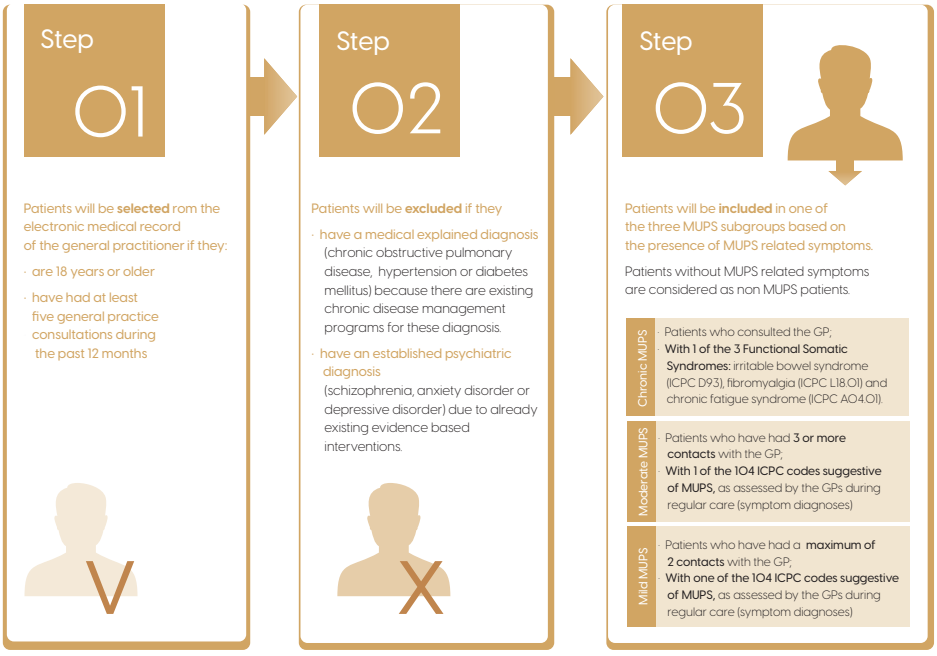

Figure 1. PRESUME screening method.

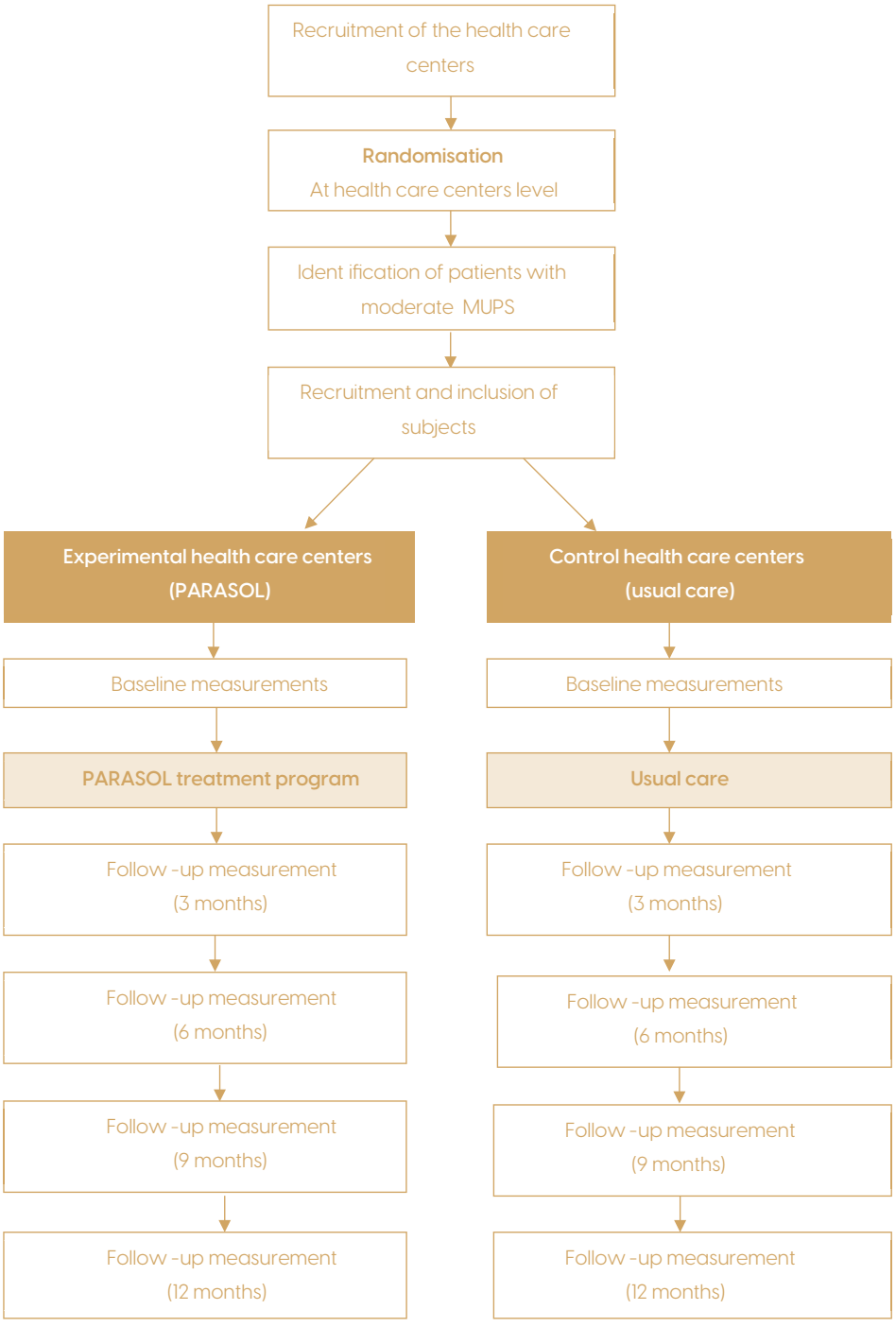

Figure 2. Overview of the study.

This is a 12-week program consisting of 4 face-to-face consultations with the mental health nurse and 5 physical therapy sessions, which are supplemented with a Web-based program (e-Exercise). Blended care has already proven to be effective in other studies [20,21] and it helps to promote self-management.

The primary objective of the present study is to investigate the effectiveness of the proactive, blended and integrated mental health and physical therapy care program (PARASOL) on impact of symptoms, as well as the physical and mental dimensions of quality of life in patients with moderate MUPS in comparison with usual care. Secondary objectives are to study the effect on severity of (psychosocial) symptoms, general health, physical behavior, illness perception, and self-efficacy in patients with moderate MUPS as well as to determine the cost-effectiveness of this program.

Methods

Study Design

A prospective, multicenter cluster randomized clinical trial will be conducted. The study has been approved by the Medical Ethical Committee of University Medical Center Utrecht, the Netherlands. The blended PARASOL intervention will be compared with usual care. An overview of the study procedure is shown in Figure 2.

Participants

Patient selection

Patients with moderate MUPS will be identified in the participating practices using 3 strategies. The first strategy is to use the PRESUME screening method. All patients in the routine care database of a GP are anonymously screened in a stepwise selection, based on a consultation frequency above five, with exclusion of chronic diseases (eg, chronic obstructive pulmonary disease, hypertension or diabetes mellitus) and psychiatric diagnoses (eg, schizophrenia, anxiety disorder or depressive disorder) and the presence of any of the 104 MUPS related International Classification of Primary Care codes. The prognostic accuracy of this PRESUME screening method for identification of moderate MUPS patients is moderate [19].

Since the PRESUME screening method is over inclusive and not meant to set an accurate diagnosis of MUPS in individual patients, all identified patients with moderate MUPS will be screened by their GP for eligibility [19]. As a consequence, the expected prevalence of patients with moderate MUPS is less than the 2.4% according to the PRESUME screening method [19]. The GP will exclude patients based on the following criteria: (1) having

another chronic somatic or psychiatric disease, (2) receiving a medically explained diagnosis between identification using the PRESUME screening method and the time of inclusion, (3) having complaints with a duration of less than 1 month, in which case further diagnostic evaluation of the symptoms is needed, and (4) unable to participate as determined by the GP, due to a life-threatening condition, a shortened life expectancy, a major life event in the past month or a MUPS targeted multidisciplinary intervention in the past 12 months.

All remaining eligible patients will proactively be approached by their GP, by sending them an invitation letter with study information.

Secondly, GPs will recruit patients during consultations if they meet the following criteria: ≥18 years of age, ≥5 general practice consultations during the past twelve months, medically unexplained physical symptoms, and the diagnostic phase is completed. When a patient is eligible, the GP can give the contact details of the researchers of the PARASOL study to the patient.

The last strategy will be open recruitment in participating health care centers. Flyers with information about the PARASOL study will be provided in the waiting rooms and included in the newsletter of the health care centers. Patients who are willing to participate can contact the researcher by phone or by mail. Subsequently, the researcher will determine whether the patient is eligible by asking if the patient is older than 18 years, has had ≥5 general practice consultations during the past twelve months, and if the patient has medically unexplained physical symptoms.

All patients who are willing to participate in the PARASOL study, will have to have access to the internet and have mastered the Dutch language. When a patient is willing to participate, they can contact the researcher by phone or email. The researcher will answer any possible questions, give further information, and will make an appointment for the patient to sign informed consent and a baseline measurement evaluation. Additionally, patients in the intervention group will be invited to participate in the blended PARASOL intervention

Study centers

The Leidsche Rijn Julius Health Care Centers (LRJG; 5 health care centers with 40,000 patients) and the Eindhoven Corporation of Primary Health Care Centers (SGE; 10 health care centers, 70,000 patients) will participate in the study. All relevant disciplines–general practitioners, physical therapists, and mental health nurses–are available and willing to participate.

Randomization Procedure

Cluster randomization will be performed at the level of the participating health care centers. Health care centers will randomly be assigned to either the intervention group or the control group (usual care) using a Web-based random generation of a sequence of numbers. Through cluster randomization, we will avoid professionals within one health care center offering both the blended PARASOL intervention and usual care, as this could cause potential contamination effects [22]. A higher drop-out rate in the intervention group is expected since psychological therapies have a 7% higher proportion of drop outs compared with usual care [18]. The blended PARASOL intervention combines both mental health and physical therapy sessions. Therefore, an unequal randomization on cluster level will be conducted. Of the 15 included health care centers, 8 will be randomized to the blended PARASOL intervention and 7 will be randomized to the control group. After randomization of the health care centers, the selection and inclusion procedure of patients with moderate MUPS will be performed.

Intervention Program

The health care program is a proactive, blended, and integrated care program offered by a physical therapist and mental health nurse. The program will start with a physical approach since patients' perception of the symptoms usually has a somatic focus and MUPS patients are often reluctant to accept psychological oriented treatments [23,24]. The aim of the health care program is to reduce complaints of moderate MUPS, stimulate self-management, and prevent chronic MUPS. The health care program is focused on patients' insight, perception of symptoms, and modifiable prognostic risk factors for the development of chronic MUPS, using a cognitive behavioral approach and therapeutic neuroscience education as well as encouraging self-management and an active lifestyle using graded activity (details are provided in Multimedia Appendix 1). It consists of 3 steps and the face-to-face sessions will be integrated with eHealth modules, called blended health care. The content of the eHealth modules will be discussed during the face-to-face sessions. Details of the 3 steps are listed below:

1. Intake: The program will start with an intake session with both the physical therapist and the mental health nurse. During the intake session the complaints, treatment goals, treatment demand, and perpetuating factors of the patient will be identified according to the somatic, cognitive, emotional, behavioral, and social factors (SCEGS) model [3]. After the intake the physical therapist and mental health nurse discuss the complaints, treatment goals, and treatment demand.

a. The physical therapist will focus on the somatic complaints (ie, physical symptoms, duration and course of symptoms, severity of symptoms, and physical

functioning) and will conduct a physical examination to get insight to factors that are related to the content of the health care program (eg, posture and movement, breathing patterns, and muscle tension) and to determine if symptom specific exercises are needed.

b. The mental health nurse will focus on cognitive, emotional, behavioral and social complaints.

2. Face-to-face sessions:

a. Patients will have 4 face-to-face sessions with the physical therapist (week 1, week 3, week 6 and week 12) where the focus will be on the perception and acceptation of physical complaints of the patients. The physical therapist will start with education regarding the unexplained symptoms. Therapeutic neuroscience education according to the sensitization model is of particular interest due to patient's somatic fixation and anxiety for a severe disease [17]. Concurrently, graded activity will be used to gradually expand activities performed by the patient using principles of operant conditioning [25,26]. The graded activity schedule can be performed in daily life. In week 6, the physical therapist will discuss the patients' lifestyle (eg, exercise, sleep, and relaxation) with the focus on behavioral changes to promote a healthy lifestyle. In week 12, the physical therapist will discuss long-term goals as well as how patients can maintain a physically active lifestyle.
b. Patients will have 3 face-to-face sessions with the mental health nurse (week 1, week 3, and week 6). In all 3 face-to-face sessions the mental health nurse will train coping strategies according to perpetuating factors and operant conditioning [25], with the focus on changing perception and acceptation. The mental health nurse will start with education regarding general perpetuating factors with the link to possible perpetuating factors of the patient. In the next 2 face-to-face sessions, the link between the perpetuating factors and patients coping strategies will be made, with the focus on behavioral change.

3. eHealth modules: The Web-based part of the health care program consists of exercises (instruction videos) and information modules on self-management and educative themes (description and videos). The modules consist of 3 components which are listed below.

a. Graded activity, an activity-focused method with operant conditioning behavioral principles with 3 consecutive phases. In the starting phase, the patient will choose an activity they want to expand gradually. The patient will perform the

chosen activity to their tolerance level (ie, until pain or fatigue drives them to stop; this will be pain-contingent) while their performance is recorded in distance units, time, or number of repetitions. After at least 3 pain-contingent measurements, occurring over several days, a baseline will be determined, and the patient sets his or her individual treatment goal. In the treatment phase, the chosen activity will be increased gradually (ie, time-contingent) and an individual scheme will be drawn up. In the integration phase, patients will be stimulated to adhere to the activity in their daily living [25,26]

b. Videos of prescribed home exercises by their physical therapist
c. Videos and information on self-management and educational themes such as central sensitization, perpetuating factors, graded activity, behavioral change, stress, coping, relaxation, lifestyle advice, creating and performing an exercise plan, and avoiding a relapse.

Usual Care

Patients in the control health care centers will get care as per usual without any restrictions. This care could include care of the GP, physical therapist, mental health nurse, and psychologist.

Outcomes

Primary Outcomes

The primary outcome measures are impact of symptoms and quality of life.

Secondary Outcomes

Several secondary parameters will be measured to determine the influence of the blended e-Exercise health care program on severity of physical and psychosocial symptoms, general health, physical behavior, illness perceptions, self-efficacy, and cost-effectiveness.

Measurements

Three time points (baseline, 3-month, and 12-month follow-up) will be used for data collection. In addition, cost questionnaires will also be sent to the patients at 6 and 9 months. Furthermore, the impact of symptoms will be measured weekly between 0 and 3 months, followed by monthly measurements between 6 and 12 months. We offer no financial incentives to complete questionnaires or to carry the Activ8 activity monitor. The measures that will be collected are listed below and Table 1 gives a summary of all measures that will be collected.

- Impact of symptoms, which addresses adequate relief using a validated single question, which is scored on a dichotomous scale ("Over the past week have you had adequate relief of your symptoms?") [27,28]. A responder for adequate short-term relief is defined as a patient who will report adequate relief of their symptoms for at least six of the twelve weeks between the baseline and three-month follow-up. In addition, a responder for adequate long-term relief will report adequate relief of their symptoms for at least three of the six months between the 6- and 12-month follow-up. Otherwise, a patient will be defined as a nonresponder. Adequate relief is a validated clinically relevant endpoint and is defined at the point where the individual patient is satisfied with treatment [29].
- Quality of life will be measured with the 36-Item Short Form Health Survey (RAND-36) health survey. The RAND-36 is a valid and reliable self-reported questionnaire [30]. The questionnaire consists of eight subscales, namely physical functioning, social functioning, role-physical or emotional problems, mental health, vitality, bodily pain, and general health. A higher score on the scale of 0-100 indicates a better quality of life [30,31].
- Severity of symptoms, defined as self-perceived pain and fatigue in the past week, will be measured with an 11-point numeric scale (score 0-10) [32].
- Severity of psychosocial symptoms will be measured with the Four-Dimensional Symptom Questionnaire (4DSQ) questionnaire. This questionnaire consists of 4 subscales, namely distress, depression, anxiety, and somatization [33,34].
- Self-perceived health will be measured with the EuroQol-5D (EQ5D) questionnaire. This questionnaire will measure the perceived health on five levels (ie, mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) [35].
- Physical movement behavior will be measured with the Activ8 activity monitor [36]. The Activ8 is a validated activity monitor to measure physical behavior by measuring several activities and postures (lying, sitting, standing, walking, running, and cycling). Patients will wear the Activ8 activity monitor for 1 week at varying intervals during the study. They will wear it at baseline, at 3 months follow-up, and at 12 months follow-up.
- Illness perceptions will be measured using the Brief Illness Perception Questionnaire. This questionnaire is an eight-item scale designed to assess cognitive and emotional representations of illness on an ordinal scale (0-10) [37,38].
- Self-efficacy will be measured with the Hei-Q questionnaire, which is a user friendly, valid, and reliable questionnaire specifically developed to evaluate patients' education and self-management programs for patients with chronic complaints [39].
- Health care use and indirect costs through illness and absenteeism will be measured with Trimbos/iMTA Questionnaire for Costs associated with Psychiatric

Illness (TIC-P) questionnaire to evaluate the cost-effectiveness of the program in terms of costs per Quality Adjusted Life Years (QALYs) [40]. Patients will be asked to complete the cost questionnaire every 3 months, since this questionnaire focuses on health-related costs in the past 3 months. QALYs will be measured using the EQ-5D scores [41]. In this way, we will get information of patients' healthcare utilization and (unpaid) productivity losses.

- Besides the above parameters, the efficacy, barriers, and facilitators of the Web-based component of the blended PARASOL intervention from a patient's perspective will be measured using the System Usability Scale (SUS). The SUS will be completed by patients of the intervention group at the end of the health care program (3-month follow-up). The questionnaire will measure the perceived usability by ten statements which can be scored on a 5-point Likert scale ('totally agree' to 'totally disagree'). The SUS is a simple, valid, and reliable measurement and is often used the evaluate the usability of eHealth applications [42].

Other Measures

Demographic and clinical variables such as age, gender, education level, work situation, duration of complaints, and possible comorbidities will be measured at baseline. Possible comorbidities will be measured again at 3 and 12 months after baseline to determine if patients have developed comorbidities or any chronic MUPS syndromes such as fibromyalgia, chronic fatigue syndrome, or irritable bowel syndrome.

Sample Size

The number of eligible patients was calculated according to Campbell et al for cluster randomized trials [43]. The power calculation is based on an intracluster correlation coefficient of 0.04 [44,45] and a minimum of 20 patients per health care center. Additionally, we assume a minimal clinical detectable change of >10 points in the sum score of physical functioning of the RAND-36 questionnaire, and a SD of 23.8 [10]. Based on these assumptions and a power of 80% (alpha=.05), at least ten health care centers and 206 participating patients are needed. With an expected drop-out rate of 20%, a total of 248 participating patients (124 patients per arm) are needed for the study

Statistical Analysis

Statistical analysis will be performed using IBM SPSS 22. Statistical analysis will be performed according to the intention-to-treat principle. Any missing values will be imputed with the Multivariate Imputation by Chained Equations. Descriptive statistics will be used to describe the number of patients with moderate MUPS (as identified using the PRESUME screening method) which are excluded by their GPs, how many patients are recruited with the 3 different strategies, as well as how many patients do not complete

the blended PARASOL intervention. Additionally, descriptive statistics (frequencies, t-test and chi-square test) will be used to describe the demographic characteristics of the study population and to explore baseline comparability. Differences in effectiveness of the blended PARASOL intervention will be analyzed using longitudinal mixed methods analyses. In this way, we can correct for independence of observations within patients as well as take into account possible variations between clusters and health care professionals. Analyses will be corrected for potential confounders (eg, age, gender, and psychiatric comorbidity) and potential interactions terms (eg, age in the use of the Web-based component of the PARASOL intervention) will be checked. Furthermore, the cost-effectiveness of the blended PARASOL intervention will be clarified with an incremental cost-effectiveness ratio based on the costs per QALY. All costs measured by the TIC-P (health care use and indirect costs of illness and absenteeism) are used to calculate the incremental cost-effectiveness ratio.

Results

The components of this intervention are based on results of a literature search and focus groups with experts (general practitioners, physical therapists, mental health nurses, and psychologists) [46]. The content of the information, self-management, and exercise modules were specifically developed for the current study. The functionality of the online program used in this study is based on the blended exercise intervention for patients with hip or knee osteoarthritis (e-Exercise) [47].

Before the start of the intervention program, physical therapists and mental health nurses of the experimental health care centers received two days of training on the content of the blended PARASOL intervention. The training consisted of presentations on the study population, central sensitization, therapeutic neuroscience education, graded activity, and perpetuating factors for all professionals involved in the study. Furthermore, the training included discussion of the content of the online modules and instructions on their implementation. During the study, a follow-up training session for the therapists will be conducted to ensure adherence to the treatment protocol.

The recruitment of health care centers started in June 2016 and inclusion of patients began in March 2017. Follow-up assessments of patients are expected to be completed in March 2019.

Table 1. Summary of measures to be collected.

Outcome measures	Data collection instrument	Follow-up measurements				
		Baseline	3 months	6 months	9 months	12 months
Primary outcome measures						
Impact of symptoms[a]	Adequate Relief question	✓	✓			✓
Quality of life	36-Item Short Form Health Survey (RAND-36)	✓	✓			✓
Secondary outcome measures						
Pain	Numeric Rating Scale	✓	✓			✓
Fatigue	Numeric Rating Scale	✓	✓			✓
Severity of psychosocial symptoms	Four-Dimensional Symptom Questionnaire	✓	✓			✓
General health	EuroQol-5 Dimensions	✓	✓			✓
Physical behaviour	Activ8 activity monitor	✓	✓			✓
Illness perceptions	Brief Illness Perception Questionnaire	✓	✓			✓
Self-efficacy	Health Education Impact Questionnaire	✓	✓			✓
Cost-effectiveness	Trimbos and iMTA questionnaire on Costs associated with Psychiatric illness	✓	✓	✓	✓	✓
Barriers and facilitators of the blended e-Exercise health care program	System Usability Scale		✓			
Other measures						
Age	Questionnaire	✓				
Gender	Questionnaire	✓				
Education level	Questionnaire	✓				
Work situation	Questionnaire	✓				
Duration of complaints	Questionnaire	✓				
Possible co-morbidities	Questionnaire	✓	✓			✓

[a]*Measured weekly between baseline and 3 months follow-up, and monthly between 6 and 12 months follow-up.*

Discussion

In this randomized clinical trial, the effectiveness (including cost-effectiveness) of the PARASOL intervention, a proactive blended and integrated mental health and physical therapy intervention program, will be studied.

Although the study is well-planned and involves all relevant stakeholders, the conduction of the study will present several operational challenges. The first challenge has been identified as GPs motivation to actively participate in the recruitment of patients with moderate MUPS. Patients with MUPS are a difficult patient group for GPs and often the patient-doctor relationship is under pressure due to mismatches between the expectations of the patient and doctor [48]. To motivate GPs to recruit patients with moderate MUPS, information about the PARASOL study will be sent to them beforehand. During the study, GPs will be individually informed if one of their patients is participating in the PARASOL study. Furthermore, all participating GPs will be sent updates at 3-month intervals informing them about total patient inclusion in the study, as well as patient inclusion per GP.

A second challenge identified is the recruitment of adequate patient numbers to achieve the desired statistical power. Patients with moderate MUPS will be identified using the PRESUME screening method, following which they will be proactively approached by their GP. This proactive approach may lead to patients in a non-symptomatic phase or without a treatment demand being contacted. Consequently, these patients might be less motivated to follow the blended PARASOL intervention aiming to prevent chronicity of MUPS. To deal with this challenge, setting individual treatment goals has been identified as an important part of the intake session. It should be noted that the face-to-face sessions are not performed on a weekly basis to not only reduce the burden for patients, but more importantly to encourage self-management.

A third challenge is the potential drop-out rate in the control group since these patients will not be receiving the blended PARASOL intervention and therefore may be less motivated to participate in the study. To deal with this challenge, patients in the control group will be offered to follow the blended PARASOL intervention after the study ends.

A final identified challenge is the non-usage of the Web-based component of the blended PARASOL intervention. Previous studies have shown that patients in online interventions are less motivated and feel less pressure to continue with the intervention compared to face-to-face interventions [49]. To combat this, patients will receive email

reminders for the eHealth modules weekly. Furthermore, the PARASOL intervention has been designed as a blended care program, and this is therefore expected to maximize adherence compared to self-guided internet interventions [50].

Besides these challenges, there are several strengths and limitations in the design of the study that should be noted. The first strength of this study is that physical therapists and mental health nurses will participate in two days of intensive training about the content of the blended PARASOL intervention. This will minimize the differences in the care offered by professionals at different health care centers during the health care program [51]. In addition, a meeting with the participating physical therapists and mental health nurses will be organized after 6 months to discuss the content of the blended PARASOL intervention as well as any possible difficulties faced. The 12-month follow-up measurement is another strength of this study as it will result in data being obtained about long-term effectiveness (and cost-effectiveness) of the program. The PARASOL intervention stimulates self-management by focusing on achieving a healthier lifestyle as well as the adoption and maintenance of exercise behavior. Since the process of adopting a change to maintaining a change takes at least six months, a long-term follow-up is of particular interest [52]. A third strength of this study is performing cluster randomization at the level of the health care centers as this ensures that a contamination-effect will be avoided [22]. Finally, this is the first study, to the best of our knowledge, that investigates the effectiveness of an intervention program for patients with moderate MUPS to prevent chronicity.

The first identified limitation of this study, is that it is unblinded. Patients, health care professionals, and the researchers are aware all of the group allocated to the blended PARASOL intervention. This may lead to bias mechanisms such as response bias or observer bias being present in the data [53]. One of the aims of the training provided to the healthcare professionals involved in the study is to avoid response bias from the health care professionals. Observer bias will be avoided by using a measurement protocol, well trained observers, and standardized outcome measures. A second limitation is that overtreatment may occur since not all patients with moderate MUPS will be prevented from developing chronic MUPS after completing the PARASOL intervention. This could lead to higher health care costs if patients are still consulting health care professionals after completing the PARASOL intervention. However, an early intervention for patients with moderate MUPS may lead to a decrease of direct and indirect costs on long term if chronic MUPS is prevented. Therefore, one of the secondary objectives is to determine the cost-effectiveness of the PARASOL intervention. A third limitation is complexity of the design of the study due to the use of cluster randomization. Cluster randomized trials are more complex, require more

patients to obtain equivalent statistical power, and require more complex analysis [43]. However, in the sample size calculation and statistical analysis, this possible design effect has been taken into account.

This study is the first trial that investigates the effectiveness (including cost-effectiveness) of a blended care program in patients with moderate MUPS. Therefore, this study will provide relevant results regarding short- and long-term effectiveness of a multidisciplinary, blended care program to prevent chronic MUPS.

Multimedia Appendix 1

Schematic view of the blended health care program		
Intake	Physical therapist	Anamnesis and physical examination
		Providing information about the web-based part of the health care program
	Mental health nurse	Anamnesis according to the SCEGS
Week 1	Physical therapist	Education about therapeutic neuroscience education
		Providing information about the 3-day baseline self-test
	Mental health nurse	Education about perpetuating factors
	Web-based component	Module 1: Central sensitisation & perpetuating factors
		Performance of a 3-day baseline test
Week 2	Web-based component	Module 2: Graded activity & Behavioural change
Week 3	Physical therapist	Evaluation of education week 1
		Education about graded activity
		Evaluation results from the 3-day self-test
		Determining short term goal
		Discussing the gradual increase of the selected activity
	Mental health nurse	Patient specific inventory on perpetuating factors
		Education about coping strategies
	Web-based component	Starting gradually increase selected activity
Week 4	Web-based component	Module 4: Stress
Week 5	Web-based component	Module 5: Coping with physical complaints
Week 6	Physical therapist	Evaluation of graded activity
		Evaluation of online modules
		Coaching on lifestyle
	Mental health nurse	Evaluation of perpetuating factors
		Evaluation of the coping strategies
Week 7	Web-based component	Module 7: Relaxation
Week 8	Web-based component	Module 8: Lifestyle
Week 9	Web-based component	Module 9: Creating an exercise plan
Week 10	Web-based component	Module 10: Performing the exercise plan
Week 11	Web-based component	Module 11: Maintaining an active lifestyle and avoiding a relapse
Week 12	Physical therapist	Discussing long-term goals
		Support to maintain a physically active lifestyle

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Chapter 5

Quality of life in patients with moderate MUPS

Based on:
Quality of life in primary care patients with moderate medically unexplained physical symptoms

Qual Life Res.
2020 Mar;29(3):693-703.

Paula E. van Westrienen
Martijn F. Pisters
Suze A.J. Toonders
Marloes Gerrits
Niek J. de Wit
Cindy Veenhof

Abstract

Background

Medically Unexplained Physical Symptoms (MUPS) have a large impact on patient's quality of life. Most studies have been limited to chronic MUPS and thus, little is known about moderate MUPS. Improved knowledge concerning determinants influencing quality of life in moderate MUPS patients can be helpful in managing MUPS. This study is aimed at describing the common characteristics seen in moderate MUPS patients and compare them with characteristics seen in chronic MUPS patients and general population. We also identified determinants of the physical and mental components of quality of life in moderate MUPS patients.

Methods

In a cross-sectional study, moderate MUPS patients (n = 160) were compared with chronic MUPS patients (n = 162) and general population (n = 1742) based on demographic characteristics and patient's quality of life. Multivariable linear regression analyses were performed to identify determinants associated with a patient's quality of life, assessed with the RAND-36.

Results

Moderate MUPS patients experienced a better quality of life than chronic MUPS patients, but a worse quality of life as compared to the general population. Determinants associated with the physical and mental components of quality of life explain 49.1% and 62.9% of the variance, respectively.

Conclusion

Quality of life of patients with MUPS varies with MUPS disease stage. Based on their quality of life scores, moderate MUPS patients would be adequately distinguished from chronic MUPS patients. Half of the variance in the physical component and almost two thirds of the mental component would be explained by a number of MUPS-related symptoms and perceptions.

Introduction

Approximately, 25–50% of the symptoms for which patients consult a general practitioner (GP) cannot be explained after adequate examination [1, 2]. These symptoms, predominantly consisting of musculoskeletal pain, dizziness and fatigue [3], can be defined as Medically Unexplained Physical Symptoms (MUPS). MUPS occurs on a spectrum from mild, to moderate, to chronic. Patients with mild MUPS symptoms usually improve within 2 weeks [4]. Moderate MUPS symptomatology can be of any type and intensity and most patients still experience symptoms after three months [4]. Patients with chronic MUPS typically experience symptoms for at least 6 months and are usually diagnosed with a functional somatic syndrome (i.e. fibromyalgia, chronic fatigue syndrome or irritable bowel syndrome) or a somatic symptom disorder according to the Diagnostic and Statistical Manual of Mental Disorders (DSM), 5th edition [4–6]. We demonstrated that patients with mild, moderate and chronic MUPS can be adequately identified using the data from the electronic medical record of a GP.

Patients with chronic MUPS have high consultation rates [5, 7–9]. During these consultations, GPs frequently focus on exclusion of a somatic disease [10]. They face difficulty in timely recognition of MUPS and an adequate MUPS diagnosis is challenging for a GP [11, 12]. The delicate balance between an appropriate diagnostic workup, preventing over testing and safeguarding the doctor–patient relationship in patients with unexplained symptoms makes adequate MUPS management even more challenging [13–15]. Therefore, preventing chronic MUPS is of great interest. Early identification and treatment of patients with MUPS could improve the prognosis and prevent chronicity.

In patients with chronic MUPS, the impact of the symptoms on the quality of life, quantified in social, physical and psychological functioning, is high [8, 9, 16–19]. Quality of life is specifically impaired in older patients [20], patients with a lower educational level [21] and patients who are unemployed [22]. Pain severity [23], frequent somatization complaints [20] and a lower level of physical activity [24] have a large impact on the physical aspects affecting the quality of life. Depression and/or anxiety symptoms, poor illness perception and a lack of social support have a high impact on the psychological aspects affecting the quality of life [25–27]. Therefore, many studies have focused on interventions for patients with chronic MUPS and looked at the quality of life of these patients as the most important outcome measurement [28–33].

So far, little is known about the quality of life of patients with moderate MUPS, especially in relation to patients with chronic MUPS and the general population [34]. Knowledge concerning the factors that determine the quality of life in patients with moderate

MUPS can improve the understanding of moderate MUPS, help to develop more effective interventions and support better treatment outcomes. In this study, we focus on assessing the characteristics of patients with moderate MUPS with a dual purpose. The first objective is to describe the characteristics of patients with moderate MUPS and compare them with those of patients with chronic MUPS and the general population. The second objective is to identify the determinants of the physical and mental component of the quality of life in patients with moderate MUPS.

Methods

Design

This study was part of a randomized clinical trial for patients with moderate MUPS in primary care (PARASOL study) in the Netherlands [35]. In a cross-sectional study, we compared baseline characteristics of participants in the PARASOL study with the general population [36] as well as patients with chronic MUPS [9]. Both comparative populations were conducted in a similar target population in the Netherlands.

Study population

Patients with moderate MUPS were recruited at two primary healthcare organizations, which had a total of fifteen healthcare centres and covered 110.000 patients in the south and mid region of the Netherlands between March 2017 and April 2018. Participants were identified using three strategies based on the PRESUME (preventive screening of medically unexplained physical symptoms) criteria. The criteria were that patients needed to be 18 years or older with at least five general practice consultations, three or more of which resulting in a diagnosis suggestive of MUPS, during the past 12 months. Furthermore, patients should not have had a medical and/or psychiatric diagnosis (i.e. chronic obstructive pulmonary disease, hypertension or diabetes mellitus; schizophrenia, anxiety disorder or depressive disorder). The first strategy was identifying patients with moderate MUPS using the electronic medical records of a general practitioner according to the PRESUME screening method. All eligible patients were proactively approached by their GP via an invitation letter explaining the study. The second strategy included GPs actively recruiting patients during consultations if patients met the PRESUME criteria. The GP gave the contact information of the researcher to eligible participants. The third strategy was an open recruitment in the participating healthcare centres by placing flyers in the waiting rooms and study information in the centres' newsletters. Patients who were willing to participate were encouraged to contact the researcher by phone or by mail. Subsequently, the researcher determined which patients were eligible based on the PRESUME criteria. A more detailed description of the recruitment procedure can be found in the study protocol of the PARASOL study [35]. Patients who were interested in

participating in our study were then accepted only if they had access to the internet and had mastered the Dutch language. All of the participants gave their written informed consent after receiving detailed information about the study's aims and procedures. For the analysis, we used data collected from the baseline measurements of the 160 patients that had participated in the PARASOL study [35].

Data about the general population originated from a nationwide, population-based sample of Dutch households drawn at random from the national telephone registry [36]. The sample participant was 16 years of age or older and there were a total of 1742 respondents. The study was conducted in 1996 by the Netherlands Organization of Applied Scientific Research.

Data concerning the patients with chronic MUPS originated from a cross-sectional study that focused on the quality of life, healthcare-related costs and work-related costs [9]. Patients were recruited in general practices, outpatient clinics at general hospitals and at a secondary community mental health service between February 2005 and September 2008. Patients were included in this study if they fulfilled the criteria for an undifferentiated somatoform disorder or a chronic pain disorder according to the DSM-IV criteria. Our study included 162 participants from this chronic MUPS study.

Measurements

Patient's quality of life was assessed using a validated and reliable 36-Item Short Form Health Survey (RAND-36). The RAND-36 consists of 36 items which are divided into subcategories: physical functioning (10 items), role functioning physical (4 items), role functioning emotional (3 items), vitality (4 items), mental health (5 items), social functioning (2 items), bodily pain (2 items), general health (5 items) and health change (1 item). Scores on these items are on a nominal or ordinal scale. These raw scores were converted to scale ranging from zero to 100, with higher scores indicating a higher quality of life [37, 38]. An example of a question is: "During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities like visiting with friends, relatives?". The internal consistency of the eight subscales is moderate to high. Cronbach's alpha varies between 0.71 and 0.92 [37]. To look at the association between a patient's quality of life and independent variables, the subscales were merged into two summary component scales. The subscales of physical functioning, role functioning physical, bodily pain and general health were combined into the "Physical Component Scale" (PCS) and the subscales of social functioning, role functioning emotional, and mental health were combined into the "Mental Component Scale" (MCS). The norm-based score for the PCS and MCS was 50, where a score below 50 meant a less favourable physical and mental health state [39, 40].

We assessed the following potential determinants concerning a patient's quality of life: severity of symptoms, severity of psychosocial symptoms, illness perception "concern", and physical behaviour. Severity of symptoms, defined as self-perceived pain and fatigue, was assessed using the Numeric Rating Scale (NRS) ranging from 0 (no pain/no fatigue) to 10 (worst imaginable pain/worst imaginable fatigue) [41]. Severity of psychosocial symptoms was assessed using the Four-Dimensional Symptom Questionnaire (4DSQ) which was a self-report questionnaire consisting of 50 items assessing 4 psychosocial symptoms: distress, depression, anxiety, and somatisation [42, 43]. For example, item 27 reads "during the past week, did you feel frightened?". Response categories are classified as: "no", "sometimes", "regularly", "often" or "very often or constantly". To achieve scale scores, the responses are scored as 0 for "no", 1 for "sometimes" and 2 for the other response categories. Item scores are summated to scale scores [44, 45]. The distress scale had a score range of 0–32, the depression scale had a score range of 0–12, the anxiety scale had a score range of 0–24 and the somatisation scale had a score range of 0–32. The 4DSQ had two cut-off points that divided the scores into low, moderately high and very high, where a higher score marked an increased probability of a disorder [44, 45]. Reliability of the 4DSQ scales is high, with Cronbach's alpha ranging between 0.84 and 0.94 [42]. The illness perception "concern" was measured with the Brief Illness Perception Questionnaire (Brief IPQ). This item assessed how worried subjects were about their complaints which were rated using a 0 to 10 response scale, with 0 (not at all concerned) to 10 (extremely concerned) [46]. Physical behaviour was measured with the Activ8 activity monitor [47]. The Activ8 is an activity monitor that measures physical behaviour by measuring several activities and positions (lying, sitting, standing, walking, running and cycling). Participants carried the Activ8 activity monitor in a trouser pocket or wore it on a leg strap for 1 week. Any time when patients had at least ninety continuous minutes of zero activity were excluded from the study. Night measurements where patients were lying down and days with fewer than 10 h of wear time were also excluded [48, 49]. Data were converted into total sedentary time (average hours per day) which included any waking behaviour characterized by an energy expenditure ≤1.5 metabolic equivalents while in a sitting, reclining or lying position [50]. Along with sedentary behaviour, Activ8 data were also converted into an average amount of hours of moderate or vigorous physical activity (MVPA) to determine if participants met the Dutch Standard for Healthy Physical Activity criteria. Participants met the Dutch Standard for Healthy Physical Activity if they had at least 150 min of moderate intense physical activity every week, spread over several different days [51]. Any measured activity had to be sustained for at least ten consecutive minutes.

Patient characteristics were assessed using a self-administered questionnaire where information concerning age, gender, marital status, duration of complaints, education level and work status was collected. Marital status was divided into two categories: married or living with a partner and unmarried, divorced or widowed. Based on univariable associations, duration of complaints was divided into two categories: complaints lasting less than 2.5 years and complaints lasting 2.5 years and longer. Level of education was divided into three groups, basic (e.g. primary school and preparatory secondary vocational education), intermediate (e.g. higher secondary education and pre-university education) and high (e.g. college and university), which were derived from the standard classification of education from Statistics Netherlands [52]. A patient's work status was either employed or unemployed.

Statistical analysis

Statistical analyses were performed using IBM SPSS 22. Any missing values were imputed with the Multivariate Imputation by Chained Equations (MICE) [53]. MICE operates under the assumption that given the variables used in the imputation procedure, the missing data are Missing At Random (MAR). MICE was done by fitting models to predict missing values for a given variable based on all other observed variables, including the outcome variable. Five imputed data sets were created and developed to pooled data. The results of the five analyses were combined using Rubin's rules to produce pooled estimates of mean effects and standard deviations. Further analyses were performed with the pooled imputed data. Multicollinearity was assessed by examining the variance of inflation factor (VIF). A value of five was chosen as the maximum accepted level of VIF [54].

Descriptive statistics were used to describe the demographic characteristics of the study population. Means and standard deviations were calculated for continuous variables whereas frequencies and percentages were calculated for categorical variables. Furthermore, descriptive statistics were calculated for the eight subscales of the RAND-36. The RAND-36 subscales of patients with moderate MUPS were compared with the RAND-36 subscales found in patients with chronic MUPS and in the general population [9, 36]. Mean differences and confidence intervals were calculated to determine if there were statistically significant differences between the groups.

To assess the association of the independent parameters with quality of life, two separate univariable and multivariable linear regression analyses were performed using the PCS and the MCS as outcome variables. Linear multiple regression analyses with backward stepwise selection were performed. Variables with a p value of > 0.1 were removed. To assess the overall performance of the final model in predicting quality of life, the R^2 statistic was calculated.

Ethics

The study was approved by the Medical Ethical Committee of University Medical Center Utrecht, the Netherlands and has been registered in the Dutch Trial Register (NTR6755) [35].

Results

Demographics

Table 1 shows the distribution of demographic characteristics for the general population, patients with moderate MUPS and patients with chronic MUPS. The age distribution of the three study populations was comparable, with a mean age ranging from 45 to 48.4 years. The general population had a lower percentage of women compared to the moderate MUPS population and chronic MUPS population. In all study populations, approximately two-third of all participants were married or living with a partner. Patients with moderate MUPS had a higher educational level compared to the general population and patients with chronic MUPS. Data concerning the employment situation of the general population was not collected. Patients with moderate MUPS were more often employed as compared to patients with chronic MUPS.

Table 1 Descriptive characteristics of the study populations [9, 36]

Variable	General population[a] (n = 1742)	Patients with moderate MUPS (n = 160)	Patients with chronic MUPS[b] (n = 162)
Age, mean (SD)	47.6 (18)	48.4 (13.7)	45 (11)
Sex, female (%)	44	74.4	80.9
Marital status, married/ living with partner (%)	69	64.8	67.9
Education level, high (%)	25	33.8	22.2
Work status, employed (%)	ł	64.4	45.1

[a]*Data obtained from the study of Aaronson et al. [36], work status was not measured;*
[b]*Data obtained from the study of Zonneveld et al. [9]*

Quality of life

Table 2 presents the means and standard deviations of the RAND-36 subscales of the moderate MUPS population, the chronic MUPS population and the general population. Patients with moderate MUPS had statistically significant higher scores on six of the eight subscales of the RAND-36 compared to the chronic MUPS population, indicating that patients with moderate MUPS experienced a higher quality of life. On the subscales of role functioning emotional and mental health, no statistically significant differences were found, indicating that the more mental part of quality of life is equal for both patient groups. On all subscales, the moderate MUPS population scored lower than the general population.

Table 2 Participants' means and standard deviations on RAND-36 subscales and the differences between the moderate MUPS - and chronic MUPS population as well as the moderate MUPS and general population [9, 36]

RAND-36 subscales	Moderate MUPS population	Chronic MUPS population	General population	Differences between Moderate MUPS and:	
	(n = 160) Mean (SD)	(n = 162)[a] Mean (SD	(n = 1742)[b] Mean (SD)	Chronic MUPS Mean [95% CI]	General population Mean [95% CI]
Physical functioning	73.1 (21.8)	50.9 (23.8)	83.0 (22.8)	22.2 [17.2 ; 27.2]	- 9.9 [-13.6 ; - 6.2]
Role functioning physical	42.8 (39.4)	15.6 (27.3)	76.4 (36.3)	27.2 [19.8 ; 34.6]	-33.6 [-39.5 ; -27.7]
Bodily pain	54.6 (20.8)	33.2 (19.6)	74.9 (23.4)	21.4 [17.0 ; 25.8]	-20.3 [-24.1 ; -16.5]
General health	52.4 (17.8)	37.9 (17.7)	70.7 (20.7)	14.5 [10.6 ; 18.4]	-18.3 [-21.6 ; -15.0]
Vitality	50.0 (20.4)	33.4 (17.9)	68.6 (19.3)	16.6 [12.4 ; 20.8]	-18.6 [-21.7 ; -15.5]
Social functioning	65.6 (25.3)	49.2 (24.4)	84.0 (22.4)	16.4 [11.0 ; 21.8]	-18.4 [-22.1 ; -14.7]
Role functioning emotional	61.7 (43.1)	65.0 (42.8)	82.3 (32.9)	-3.3 [-12.7 ; 6.1]	-20.6 [-26.1; -15.1]
Mental health	66.4 (17.9)	62.7 (20.1)	76.8 (17.4)	3.7 [-0.5 ; 7.9]	-10.4 [-13.2 ; -7.6]

RAND-36 Research and Development Corporation 36-item Health Survey, SD standard deviation, CI confidence interval;
[a]*Data obtained from the study of Zonneveld et al. [9];*
[b]*Data obtained from the study of Aaronson et al. [36]*

Clinical characteristics of moderate MUPS

The clinical characteristics of patients with moderate MUPS are shown in Table 3. In total, 1.4% of the data for eight variables was missing. Missing data were Missing At Random (MAR) and imputed and analyses were performed with the pooled data. Almost seventy percent of the 160 patients with moderate MUPS had complaints lasting more than 2.5 years. Patients had a less favourable physical and mental health state compared to the norm-based score of 50, with a mean score of 42.7 (SD = 8.8) and 43.9 (SD = 12.3), respectively. In addition, patients with moderate MUPS experienced a somewhat higher level of fatigue than pain, with a mean score of 6.0 (SD = 2.5) and 5.0 (SD = 2.6), respectively. The severity of psychosocial symptoms was moderately high for the domain distress and somatization and low for depression and anxiety. The illness perception "concern" had a mean score of 5.4 (SD = 2.7). Patients were moderately or vigorously active an average of 0.5 h per day (SD = 0.48) and sedentary an average of 8.9 h per day (SD = 2.0).

Table 3 Clinical characteristics of patients with moderate MUPS

Variable	Patients with moderate MUPS (n = 160), Mean (SD)
Duration of physical complaints, 2.5 years (%)	68.8
Physical health (RAND-36; PCS)	42.7 (8.8)
Mental health (RAND-36; MCS)	43.9 (12.3)
Pain (NRS)	5.0 (2.5)
Fatigue (NRS)	6.0 (2.6)
Severity of psychosocial symptoms (4DSQ)	
Distress	12.3 (8.1)
Depression	1.7 (2.8)
Anxiety	2.9 (4.2)
Somatization	12.7 (6.8)
Illness perception "concern"	5.4 (2.7)
Sedentary behaviour (total sedentary time per day)	8.9 (2.0)
MVPA (average hours per day)	0.5 (0.5)

RAND-36 Research and Development Corporation 36-item Health Survey, PCS physical component summary, MCS Mental Component Scale, NRS Numeric Rating Scale, 4DSQ Four-Dimensional Symptom Questionnaire, MVPA moderate or vigorous physical activity

Factors associated with quality of life

The results of the univariable and multivariable regression analysis are shown in Tables 4 and 5, respectively. The assumptions for multiple linear regression were met and no multicollinearity was detected.

Physical component

In the univariate analysis, ten parameters were significantly associated with a reduced physical component of quality of life (Table 4). In multivariate comparison, seven of these parameters independently predicted the score for the physical component of quality of life (R^2 of 49.1%). Physical health increased by 5.103 when patients with moderate MUPS had a job. Physical health decreased by 0.584 for the severity of pain and 1.073 for the fatigue score for every additional point on a scale of 0–10. For the severity of psychosocial symptom measurements, domain distress, physical health increased by 0.290 for every increased point on a scale of 0–32. Moreover, for domain somatisation, physical health decreased by 0.331 for every increased point on a scale of 0–32. Physical health decreased by 0.474 for every increased point on the "concern" question of the illness perception questionnaire with a scale of 0–10. Lastly, physical health increased by 1.956 when a patient had at least 1 h of moderate or vigorous physical activity per day (Table 5).

Mental component

Eight parameters were significantly associated with the mental component of the quality of life in univariate analysis (Table 4). In a multivariable comparison, ten parameters independently predicted the mental component of quality of life (R^2 of 62.9%). The mental component of quality of life increased by 3.238 when patients with moderate MUPS were female. Mental health decreased by 0.057 when patients with moderate MUPS were older and by 2.633 when patients were unemployed. Moreover, mental health decreased by 0.785 for every increased point on a scale of 0–10 for severity of fatigue symptoms. All domains of the severity of psychosocial symptoms had associations with mental health. For every increasing point measured for the domains of distress (scale 0–32), depression (scale 0–12) and anxiety (scale 0–24), mental health decreased by 0.731, 0.846 and 0.499, respectively. Mental health increased by 0.366 with every decreased point of somatisation on a scale of 0–32. Lastly, associations were found for the parameter illness perception "concern" and average hours per day of moderate or vigorous physical activity. Mental health decreased by 0.523 for every increased point on the "concern" question of the illness perception questionnaire with a scale of 0–10. When a patient was moderately or vigorously active for 1 h per day, their mental health decreased by 2.007 (Table 5).

Table 4 Univariable associations between the physical component and the mental component of quality of life and patient characteristics (n = 160)

	Physical component				Mental component			
	B	SE B	*p*	β	B	SE B	*p*	β
Sex, female	- 1.273	1.596	0.425	- 0.063	5.576	2.189	0.011	0.199
Age	- 0.018	0.051	0.719	- 0.029	0.079	0.071	0.265	0.088
Married, living with partner	- 0.256	1.464	0.861	- 0.014	3.453	2.026	0.088	0.131
High educational level	4.316	1.436	0.003	0.233	- 0.313	2.062	0.879	- 0.012
Intermediate educational level	- 2.544	1.407	0.071	- 0.142	- 1.538	1.981	0.438	- 0.062
Employed	6.412	1.366	0.000	0.350	1.002	2.034	0.623	0.039
≥2.5 years of complaints	- 3.140	1.485	0.035	- 0.166	- 0.049	2.104	0.981	- 0.002
Severity of symptoms								
Pain	- 1.877	0.240	0.000	- 0.528	- 1.081	0.386	0.005	- 0.218
Fatigue	- 1.730	0.234	0.000	- 0.508	- 1.854	0.349	0.000	- 0.390
Severity of psychosocial symptoms (4DSQ)								
Distress	- 0.194	0.085	0.023	- 0.179	- 1.117	0.082	0.000	- 0.739
Depression	- 0.267	0.249	0.284	- 0.084	- 2.905	0.262	0.000	- 0.661
Anxiety	- 0.350	0.165	0.034	- 0.831	- 1.519	0.197	0.000	- 0.523
Somatisation	- 0.556	0.094	0.000	- 0.430	- 0.486	0.139	0.000	- 0.268
Illness perception "concern"	- 1.298	0.239	0.000	- 0.400	- 1.644	0.337	0.000	- 0.361
Average hours per day:								
Of sedentary time	- 0.117	0.354	0.741	0.003	0.246	0.528	0.642	0.041
Of moderate or vigorous physical activity	4.724	1.637	0.005	0.188	3.407	2.070	0.100	0.057

B unstandardized regression coefficient, SE standard error of the estimate, standardized regression coefficient, e variable excluded from the regression model

Table 5 Multivariable associations between the physical component and the mental component of quality of life and patient characteristics (n = 160)

	Physical component				Mental component			
	B	SE B	*p*	β	B	SE B	*p*	β
Constant	50.958	2.141	0.000		61.613	4.472	0.000	
Sex, female	e				3.238	1.553	0.037	0.115
Age	e				- 0.057	0.053	0.282	- 0.064
Married, living with partner	e				e			
High educational level	e				e			
Intermediate educational level	e				e			
Employed	5.103	1.119	0.000	0.278	- 2.633	1.510	0.081	- 0.103
≥2.5 years of complaints	e				e			
Severity of symptoms								
Pain	- 0.584	0.278	0.036	- 0.164	e			
Fatigue	- 1.073	0.278	0.000	- 0.315	- 0.785	0.331	0.018	- 0.165
Severity of psychosocial symptoms (4DSQ)								
Distress	0.290	0.081	0.000	0.268	- 0.731	0.156	0.000	- 0.483
Depression	e				- 0.846	0.386	0.029	- 0.193
Anxiety	e				- 0.499	0.211	0.018	- 0.172
Somatisation	- 0.331	0.097	0.001	- 0.255	0.366	0.124	0.003	0.202
Illness perception "concern"	- 0.474	0.228	0.037	- 0.146	- 0.523	0.276	0.059	- 0.115
Average hours per day:								
Of sedentary time	e				e			
Of moderate or vigorous physical activity	1.956	1.212	0.107	0.106	- 2.007	1.495	0.180	- 0.078
R^2 statistic	0.491				0.629			

B unstandardized regression coefficient, SE standard error of the estimate, standardized regression coefficient, e variable excluded from the regression model

Discussion

In this cross-sectional study, the characteristics of patients with moderate MUPS were compared to the characteristics of patients with chronic MUPS and the general population. We found significant and consistent differences in the quality of life between the patients with moderate MUPS, those with chronic MUPS and the general population. Our data demonstrate a continuum in the quality of life of the three groups, with patients with moderate MUPS experiencing a better quality of life than patients with chronic MUPS but a worse quality of life as compared to the general population. The general population scores for all of the quality of life domains were significantly higher than the scores for the patients with moderate MUPS. In comparison with patients with chronic MUPS, patients with moderate MUPS had a significantly better quality of life for most domains with the exception of emotional functioning and mental health for which no differences were found between moderate and chronic MUPS patients. Our findings indicate that patients with moderate MUPS differ from the general population and patients with chronic MUPS based on their quality of life. Furthermore, differences in the quality of life scores among the three groups varied for most domains measured on a scale between 10 and 33 points, indicating a clinically relevant difference [55]. Therefore, patients with moderate MUPS can be seen as a clinical relevant group. In addition, we also identified which factors were associated with the physical and mental components of the quality of life in patients with moderate MUPS. Factors associated with the physical and mental components of quality of life are gender, age, work status, severity of pain and fatigue, the four domains of severity of psychosocial symptoms, the illness perception "concern" and the average hours per day of MVPA, which explain 49.1% of the variance in the physical component of quality of life and 62.9% of the variance in the mental component of quality of life. The physical component of quality of life is best explained by the severity of fatigue and poorly explained by the average hours per day of MVPA with a beta of - 0.315 and 0.106, respectively. The mental component of quality of life is best explained by the severity of the psychosocial symptom distress and poorly explained by age with a beta of - 0.483 and -0.064, respectively.

Our explained variance in the mental component of the quality of life is distinctly higher as compared to other studies [56, 57]. This could be due to the fact that some factors measured the same domain as mental health (e.g. distress, depression and anxiety), but no multicollinearity was detected. Key determinants were comparable to the chronic MUPS population. Previous studies reported that patients with chronic MUPS often experience a lower quality of life when they are older and unemployed [22, 25]. In addition, patients who had more depressive symptoms, more anxiety symptoms, more somatisation symptoms along with severe pain also experienced a lower quality of life [20, 23–25, 58].

Many of our findings were comparable to previous studies but some were surprising. More distress was associated with better physical functioning in our study. Patients with an increased severity of distress could have been overloaded but since they also had a low level of disability, they still had a high level of physical functioning. Furthermore, better mental functioning was experienced when patients had more somatisation complaints. It could be that patients with an increased severity of somatisation had fewer mental complaints since they attributed their complaints to their physical illness.

Our study has a number of strengths and limitations. One strength is that the study populations came from the same target population in the Netherlands. Another strength is the fact that this is the first study, as far as we know, that focused on patients with moderate MUPS and compared this study population with the general population and the chronic MUPS population. Since little is known about the moderate MUPS population, new insights are valuable in tailoring strategies in the management of MUPS and in preventing chronicity. Along with these strengths, some limitations should also be noted. One limitation is that data concerning the quality of life of the general population was based on a study conducted in 1996 while data collected on chronic MUPS is from 2005 to 2008. Given the fact that these data are over 20 and 10 years old, respectively, this may raise the question as to whether these findings are still representative. These studies are, however, still the best available nationwide population-based samples. A second limitation is that the three study populations differed on some of the descriptive characteristics. Patients with moderate MUPS had a higher educational level and were more often employed. Furthermore, the study populations of patients with moderate MUPS and chronic MUPS had a higher percentage of women as compared to the general population. In regards to gender, the general population was an acceptable reflection of the current Dutch population. The higher percentage of females in the two MUPS populations can be explained by the fact that patients with MUPS are more often female [59, 60].

In conclusion, the quality of life of patients with MUPS varies with MUPS disease stage. Based on their quality of life scores, patients with moderate MUPS would be adequately distinguished from those with chronic MUPS. Half of the variance in the physical quality of life component and almost two-thirds of the mental quality of life component would be explained by a number of MUPS- related symptoms and perceptions. The focus of future research should be on improved management of patients with moderate MUPS and more specifically, whether or not chronicity can be prevented in patients with moderate MUPS.

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Chapter 6

Effectiveness of the PARASOL intervention – a cluster RCT

Based on:
Effectiveness of a blended multidisciplinary intervention for patients with moderate medically unexplained physical symptoms (PARASOL): a cluster randomized clinical trial

In preparation

P.E. van Westrienen
N.J. de Wit
S.A.J. Toonders
C. Veenhof
M.M.J.G Gerrits
M.F. Pisters

Abstract

Background

In patients with moderate Medically Unexplained Physical Symptoms (MUPS), an intervention should focus on both physical and psychological aspects. A proactive, blended and integrated physical therapy and mental health nurse intervention (PARASOL) might reduce complaints, stimulate self-management and prevent chronicity.

Objective

To investigate short- and long-term effectiveness of the PARASOL intervention compared to usual care in patients with moderate MUPS presenting in primary care.

Methods

We conducted a cluster randomized clinical trial. The twelve week intervention integrated 5 face-to-face sessions with the physical therapist, 4 with the mental health nurse and access to a web-based program consisting of graded activity, exercises and information modules. Primary outcomes were the subjective symptom impact, as registered with the adequate relief question, and quality of life. Secondary outcome measures were severity of (psychosocial) symptoms, overall current health, physical behaviour, illness perceptions, and self-efficacy. Assessment took place at baseline, after three and twelve months.

Results

Compared to usual care (n=80), patients in the PARASOL intervention (n=80) had more adequate short-term relief (31.2% adequate relief in intervention group vs. 13.7% adequate relief in control group). On quality of life and secondary outcomes no significant between group differences on short- and long-term were found. Within the intervention group, almost half of the outcome measures had significantly improved on short- and long-term, compared to none in the usual care group.

Conclusions

A relatively short multidisciplinary intervention in primary care, integrating face-to-face sessions with a web-based program does improve subjective symptom impact of patients with moderate MUPS on short-term. No additional beneficial effects on the other outcomes were found. The intervention should be optimized and future research should confirm if the intervention is suitable for patients with moderate MUPS in primary care.

Introduction

Medically unexplained physical symptoms (MUPS) are defined as physical complaints such as pain, fatigue and/or dizziness for which no pathophysiological explanation can be found after adequate medical examination [1-3]. MUPS is classified in a continuum from mild, to moderate, to chronic MUPS [1]. The majority (75%) of the patients have mild MUPS, in whom symptoms generally recover within 1-3 months [4-6]. Twenty percent of the patients with MUPS have persisting symptoms after three months. Most of them have moderate MUPS [4], and experience severe unexplained symptoms, with psychological and physical distress, but without a diagnosis of a functional somatic syndrome (FSS), or a somatic symptom disorder (SSD) according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition [4,7]. The remaining 5% have chronic MUPS, defined by the presence of FSS, such as fibromyalgia, chronic fatigue syndrome or irritable bowel syndrome, or SSD [4,7].

Chronic MUPS has a high impact on patients' quality of life and daily functioning [8,9]. For GPs, adequate management of chronic MUPS is challenging, given the unexplained background and high consultation frequency [9,10]. For society, the high health care utilization in chronic MUPS creates a financial burden [9,11]. Because of the high impact of chronic MUPS there is a need for early identification of patients with moderate MUPS and (cost-)effective interventions to prevent chronicity.

We recently demonstrated that patients with moderate MUPS can be adequately identified using data of the electronic medical records of the GP [12]. Subsequently patients can be proactively approached by the GP for intervention. However, so far, no effective interventions for patients with moderate MUPS are known. Currently, Dutch multidisciplinary guidelines recommend focus on both physical and mental aspects in treatment [2]. The GP is suggested to act as case manager, in close collaboration with the mental health nurse and/or physical therapist with a special interest in MUPS. So far solid evidence for effectiveness of this integrated approach is lacking [2,13].

We developed a proactive, blended and integrated multidisciplinary intervention (PARASOL) for patients with moderate MUPS in primary care with the aim to prevent chronicity [14]. The intervention integrates face-to-face sessions with the physical therapist and mental health nurse with a web-based program of graded activity, information modules and exercises. This blended care approach provides patients 24/7 access to an online eCoachings platform, ensuring continuity of care and encouragement of self-management. In a randomised clinical trial we evaluated the effectiveness of the PARASOL intervention on subjective symptom impact and quality

of life of patients with moderate MUPS in primary care. Being a complex intervention we used the Medical Research Council framework for the evaluation of PARASOL [15].

Materials and Methods

Design

A prospective, multicenter cluster randomized clinical trial in primary care.

Setting and participants

Fifteen multidisciplinary health care centers, with in total 110.000 patients, participated. Patients were eligible if they were 18 years or older, had at least five GP's consultations in the past 12 months, of which three or more resulted in a diagnosis suggestive of MUPS. Furthermore, patients with a confirmed medical and/or psychiatric diagnosis (i.e. chronic obstructive pulmonary disease, hypertension or diabetes mellitus schizophrenia, anxiety disorder or depressive disorder) were excluded.

Eligible patients were approached using three strategies [12]. In the first strategy patients with moderate MUPS were identified in the electronic medical records of the GP using the previously reported PRESUME screening method [12]. All identified patients were proactively approached with an invitation letter of their GP explaining the study. In the second strategy participating GPs actively recruited patients with moderate MUPS during consultations, and - if they met the PRESUME criteria- linked them to the research group for inclusion. In the third strategy patients were recruited through flyers in the waiting rooms in the participating health care centers by placing and study information in the centers' newsletters. Patients who were willing to participate were encouraged to contact the researcher by phone or by mail. Subsequently, the researcher checked the diagnosis (moderate MUPS according to the PRESUME criteria), and confirmed that patients had access to internet and master the Dutch language. After receiving detailed information about the study's aims and procedures, patients were asked to provide written informed consent.

Intervention program

The twelve week PARASOL intervention integrates five face-to-face sessions with the physical therapist, four face-to-face sessions with the mental health nurse and access to a web-based program focusing on 1) graded activity, 2) exercises and 3) information modules (shown in Fig. 1). The components of the intervention were based on results of a literature search and focus groups with experts [16]. The web-based program was based on the e-Exercise intervention for patients with hip or knee osteoarthritis [17].

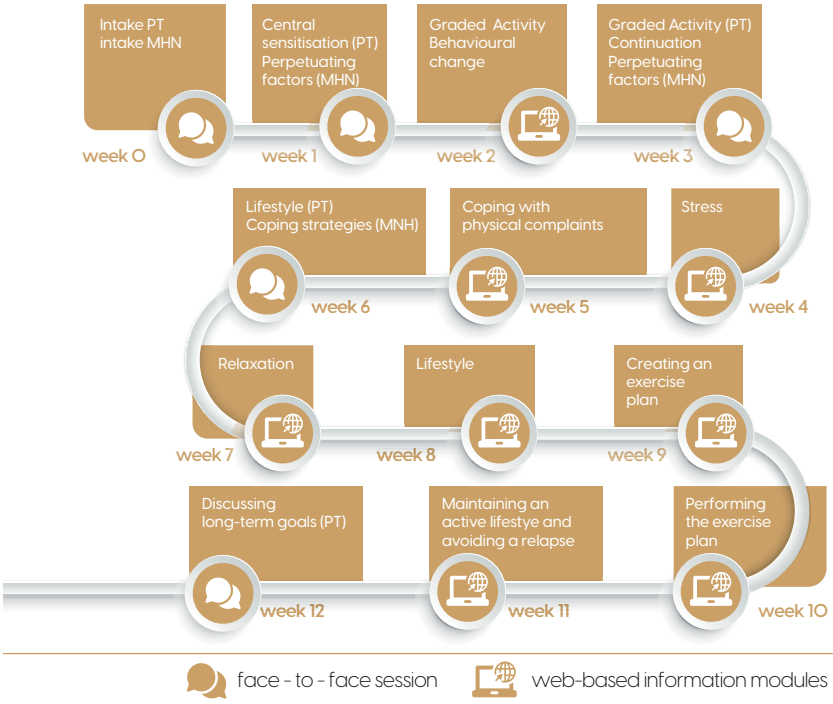

Figure 1. Overview of the PARASOL intervention. *PT, physical therapist; MHN,mental health nurse*

The intake started with the physical therapist since participants' perception of the symptoms usually has a somatic focus and patients with MUPS are often reluctant to accept a primary psychological oriented approach [18,19]. The physical therapist focused on the somatic complaints and conducted a physical examination to get insight in the physical status (e.g. posture and movement, breathing patterns and muscle tension). Afterwards, the physical therapist created an account for the web-based program and added symptom specific exercises in the web-based program and informed the participant about the first information modules with corresponding home assignments. In the second part of the intake, the mental health nurse focused on cognitive, emotional, behavioural and social aspects of the complaints [20]. Patients' treatment goals and treatment demand were also identified during the intake. After completing the intake the two professionals discussed the complaints, the background, the expectations and the treatment goals of the patient.

After the intake, participants had four follow-up sessions with the physical therapist and three with the mental health nurse, combined with home assignments in the web-based program. The home assignments and the themes of the information modules (videos and descriptions) were discussed during the face-to-face sessions.

Participants followed an online graded activity program and received instructions for exercises at home (shown in Fig. 1). Weekly automatic emails informed and reminded participants about new assignments and content. The focus of the last session with the physical therapist was on formulating a long-term goal to maintain the physically active lifestyle after the intervention.

Usual care

Usual care was defined as routine GP care for patients with MUPS, which could be provided by the GP, physical therapist, mental health nurse and psychologist, without restrictions. The physical therapists and mental health nurses of the health care centers in the control group were blinded to the intervention. After the end of the study, participants in the control group were offered to follow the PARASOL intervention.

Outcomes

Study outcomes were assessed at baseline, three months (short-term) and twelve months (long-term). Participants received a hard copy, an online questionnaire and an accelerometer. Participant characteristics such as age, gender, marital status, education level, work situation, duration of complaints, and possible comorbidities were assessed at baseline. In case a participant did not complete the questionnaires, a first reminder was sent after one week and a second reminder or a phone call after two weeks. No financial incentives were offered to complete the measurements.

Primary outcome measures

We used two primary outcomes to evaluate the PARASOL intervention. The first one was subjective symptom impact, as registered with the adequate relief question. This is a validated single question measurement, which is scored on a dichotomous scale ("Over the past week have you had adequate relief of your symptoms?") [21,22]. Adequate short-term relief was defined as a participant who reported adequate relief of their symptoms for at least six of the twelve weeks between the baseline and three-month follow-up. If not, a participant was defined as a non-responder [23]. Adequate long-term relief was defined as a participant who reported adequate relief of their symptoms for at least four of the seven months between the 6- and 12-month follow-up. The second primary outcome was quality of life, as assessed with the 36-Item Short Form Health Survey (RAND-36) health survey [24,25]. The RAND-36 consists of eight subscales, which were merged into two summary component scales: "Physical Component Scale" (PCS) and Mental Component Scale" (MCS). The norm-based score for the PCS and MCS was 50, where a score below 50 meant a less favourable physical and mental health state [26,27].

Secondary outcome measures

Symptom severity on pain and fatigue was assessed using a numeric rating scale ranging from 0 (no pain/no fatigue) to 10 (worst possible pain/fatigue) [28]. Severity of psychosocial symptoms was assessed with the Four-Dimensional Symptom Questionnaire (4DSQ) [29,30]. The questionnaire consists of four subscales, namely distress with a score range of 0-32, depression with a score range of 0-12, anxiety with a score range of 0-24 and the somatisation scale with a score range of 0-32. A higher score defines an increased probability of a disorder. Overall current health was assessed with the EuroQol visual analogue scale (EQ VAS) [31]. Scores ranged from 0 ("the worst health you can imagine") to 100 ("the best health you can imagine"). Physical behaviour was assessed with the Activ8 activity monitor [32]. The Activ8 is an activity monitor that measures physical behaviour by measuring several activities and postures (lying, sitting, standing, walking, running and cycling). Data were converted into total sedentary time and the average amount of hours of moderate or vigorous physical activity (MVPA). Total sedentary time (average hours per day) included any waking behaviour characterized by an energy expenditure ≤1.5 metabolic equivalents, while in a sitting, reclining or lying posture. MVPA was measured, to determine if participants met the Dutch Standard for Healthy Physical Activity criteria. Participants met the Dutch Standard for Healthy Physical Activity if they had at least 150 minutes of moderate intense physical activity every week, spread over several different days [33]. Illness perceptions were assessed with the Brief Illness Perception Questionnaire [34,35]. The questionnaire consists of eight items and had a score range of 0-10. Higher scores on personal control beliefs, treatment control beliefs and coherence beliefs indicates an improvement in perception, whereas on consequences beliefs, timeline beliefs, identity beliefs, concern beliefs and emotional response beliefs a lower score indicates an improvement in perception. Self-efficacy was assessed with the Health Education Impact Questionnaire. The questionnaire consists of eight subscales and were scored on a 4-point Likert scale ("totally disagree" to "totally agree") [36]. A higher score indicates a higher level of self-management.

Sample size

The required number of participants was calculated according to instructions of Campbell et al. for cluster randomized trials [37]. The power calculation was based on the primary outcome measure quality of life (power = 0.8; alpha = 0.05) using an intracluster correlation coefficient of 0.04 [38,39] and setting a minimum of 20 participants per health care center. The presumed clinical detectable change in the sum score of physical functioning of the RAND-36 questionnaire was 10 with a SD of 23.8 [40]. Thus with a power of 0.8 and an alpha of 0.05 anticipating a maximum loss to follow-up of 20% at sample size of 248 participants (124 participants per arm) is was needed.

Randomization

We used cluster randomization on health care center level to prevent contamination. Unequal randomisation through a web-based random generation of a sequence of numbers was conducted as we expected a higher drop-out rate in the intervention group [41]. Of the 15 health care centers, eight were randomized to the PARASOL intervention and seven the control group. The health care centers were informed about their allocation by email. The participating health care professionals and patients were not blinded. The main investigators were also not blinded to group assignment.

The physical therapists and mental health nurses of the health care centers assigned to the intervention group were instructed how to treat patients with moderate MUPS during a two-day training on the content of the PARASOL intervention. The physical therapists and mental health nurses of the control health care centers were not trained.

Ethics

The trial protocol and study material was approved by the Medical Ethical Committee of University Medical Center Utrecht, the Netherlands (number 16/532). The trial was registered in the Dutch trial register with number NL6581.

Participants were informed about the design and conduct of the study and asked for informed consent. They were assigned to a unique trial code and participant information was stored separately from outcome data.

Statistical analysis

Descriptive statistics were used to describe participants' general characteristics. Frequencies, t tests and chi-square tests were used to explore agreement in demographics between both groups on general characteristics. The primary analyses were performed according to the intention-to-treat principle. Per-protocol analyses were performed for participants who adhered to the PARASOL intervention and for all participants in the usual care group. Missing values were imputed with the Multivariate Imputation by Chained Equations.

We performed univariate and multivariate analyses to determine the effectiveness of the PARASOL intervention on mean differences in the primary and secondary outcome measures on short- and long-term. In both univariate and multivariate analyses, the baseline value was included as covariate [42]. In the multivariate analyses, we controlled for recruitment strategy, marital status, age and duration of symptoms, since these variables had a more than 10% change-in-estimate of the effect. The primary outcome subjective symptom impact was analyzed by logistic regression. All other

outcome measures were analyzed with a linear regression model. From these models, we estimated the mean of the outcomes for the intervention group and control group, mean differences within groups and mean differences between groups (with 95% CIs).

To determine if linear mixed model analysis with a 2-level hierarchy was necessary, heterogeneity was assessed across health care centers on quality of life as primary outcome measure by calculating the intraclass correlation coefficient (ICC). The highest ICC was found to be 0.034. Linear mixed model analyses were performed, but no variations between clusters was observed. Therefore, only univariate and multivariate intention-to-treat analyses are presented in the tables.

Per-protocol analyses consisted of multivariate analyses controlling for the same variables as the primary analyses. Additional sensitivity analyses were performed by comparing the results of the main analysis of subjective symptom impact for different cut-off points to ensure the validity of the results. On short-term when a participant reported a maximum of five times adequate relief or at least seven times adequate relief; on long term when a participant reported a maximum of three times adequate relief or at least five times adequate relief. Analyses were carried out using SPSS Statistics 25.0 (IBM SPSS, Chicago, Illinois).

Results

Participant flow

After randomisation one health care center allocated to the intervention group declined to participate due to lack of time of the health care professionals. In the remaining 14 health centers, 169 eligible patients were included between March 2017 and April 2018. Of these, 139 (82%) participants were identified through the PRESUME approach, 5 (3%) were recruited during GP's consultation and 25 (15%) via flyers in the waiting rooms and study information in the centers' newsletters. On average, five participants were included per health care center (range 2 to 34).

Nine eligible patients did not provide informed consent, because of lack of time (n=1), priority for another treatment (n=1) or other/unknown (n=7). Of the remaining 160 participants, 80 originated from health care centers allocated to the intervention group and 80 from health care centers allocated to the control group. The inclusion stopped after the originally planned 12 months because of the financial budget restrictions of the project.

Seven physical therapists and six mental health nurses from the health care centers allocated to the PARASOL intervention, were trained in the PARASOL intervention. On average they each treated 12 participants (range 5 to 26). No adverse effects of the intervention were reported.

Table 1 Characteristics of participants[a]

Characteristic		Baseline		
		All participants (n = 160)	Exp (n= 80)	Con (n = 80)
Gender	female	119 (74.4)	57 (71.3)	62 (77.5)
Age	year, mean (SD)	48.4 (13.7)	47.1 (12.4)	49.7 (14.9)
Duration of symptoms	0 mo. – 1 y.	22 (13.7)	8 (10)	14 (17.5)
	≥1 y.	138 (86.3)	72 (90)	66 (82.5)
Education level	Low	41 (25.6)	18 (22.5)	23 (28.8)
	Middle	65 (40.6)	38 (47.5)	27 (33.8)
	High	54 (33.8)	24 (30)	30 (37.5)
Work status	Student	2 (1.3)	1 (1.3)	1 (1.3)
	Employed	103 (64.4)	53 (66.3)	50 (62.5)
	Unemployed	27 (16.9)	13 (16.3)	14 (17.5)
	Retired	22 (13.8)	10 (12.5)	12 (15)
	Volunteer	6 (3.8)	3 (3.8)	3 (3.8)
Marital status[b]	Unmarried	56 (35)	22 (27.5)	34 (42.5)
	Married/living with partner	103 (64.4)	57 (71.3)	46 (57.5)
No. of co-morbidities	0	85 (53.1)	45 (56.2)	40 (50)
	1	31 (19.4)	15 (18.8)	16 (20)
	≥2	44 (27.5)	20 (25)	24 (30)
Recruitment strategy	PRESUME screening	130 (81.3)	57 (71.3)	73 (91.3)
	GP during consultation	5 (3.1)	5 (6.3)	0 (0)
	Open recruitment	25 (15.6)	18 (22.5)	7 (8.8)

[a]*Data are reported as number (percentage) of participants unless otherwise indicated*
[b]*One participant included in the experimental group refused to answer here marital status.*
Exp = experimental group, Con = control group

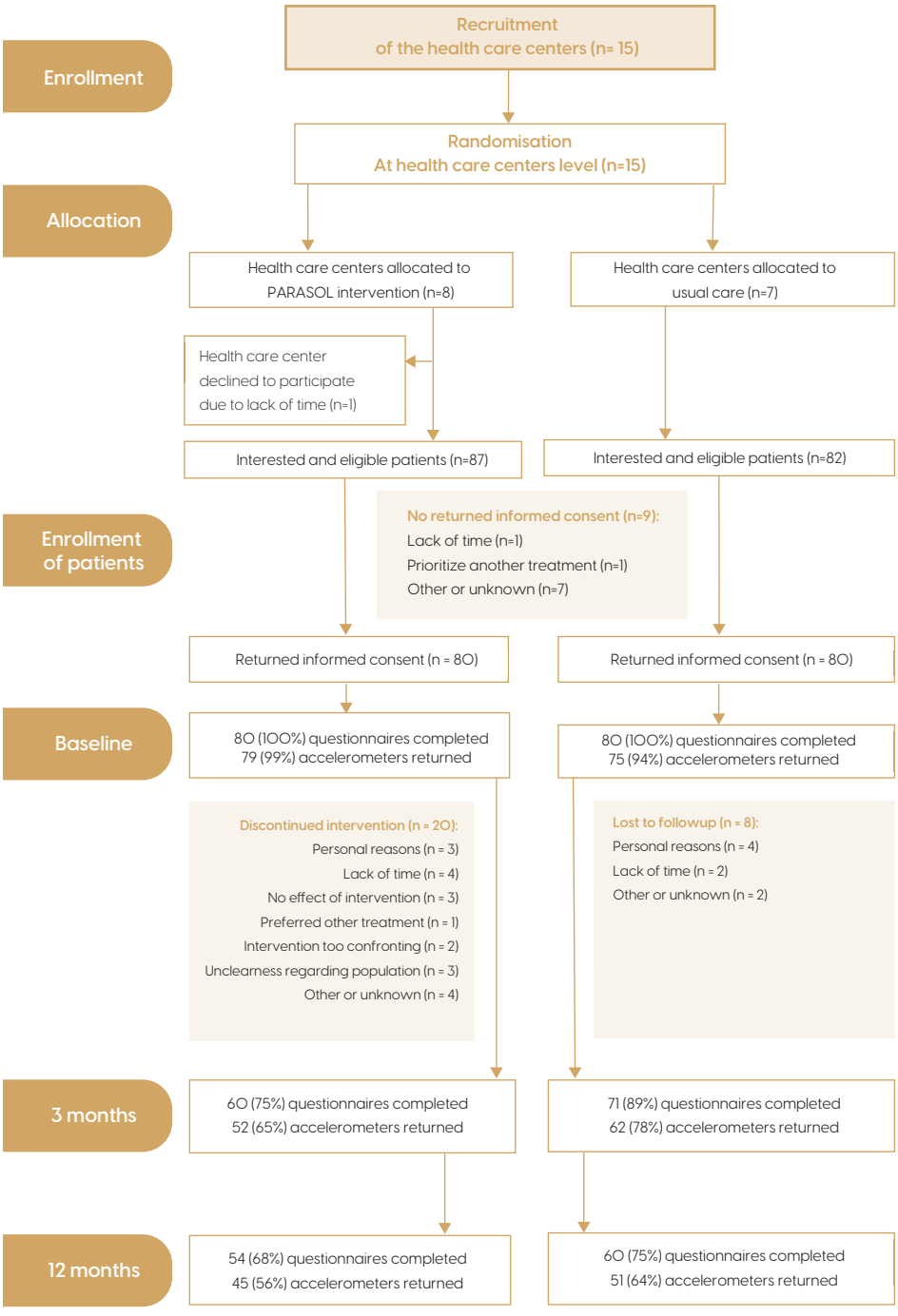

Figure 2. Flow chart

The response rate for the questionnaires was 100% at baseline, 82% at three months, and 71% at twelve months (Fig. 2). Eligible accelerometer data at baseline, three months and twelve months were available for 96%, 71%, and 60% of the 160 participants, respectively. Overall dropout rate in the intervention group was 32.5%, in the control group 25%. In the intervention group dropouts were significantly older and had a significantly shorter duration of symptoms compared to the non-drop outs. In the control group dropouts and non-dropouts did not differ. Furthermore, the two patient groups did not differ in most demographic characteristics (Table 1).

Short-term effectiveness

After completing the intervention, 31.2% of patients reported adequate relief, as compared to 13.7% in the control group (Table 2). This between group difference persisted after adjustment for recruitment strategy, marital status, age and duration of symptoms in multivariate analysis (Table 4).The quality of life of patients within the intervention group improved significantly both for PCS and MCS as compared to the control group (Table 2). Quality of life changes between the intervention and control group did not differ in adjusted analysis (Table 4). As for the secondary outcomes, patients within the intervention group improved significantly on overall current health, severity of psychosocial symptoms subscale distress and subscale somatization, and the illness perception items personal control, coherence, and emotional response (Table 3). In contrast, in the usual care group, none of the outcome measures showed any significant within group differences over time. Secondary outcome measures did not differ between intervention and control group in adjusted analysis (Table 4).

Short-term results of the per-protocol analyses showed similar results on the primary outcome measures as the intention-to-treat analyses (Table 5). Both sensitivity analyses demonstrate comparable findings on subjective symptom impact (results not presented).

Long-term effectiveness

In 12-month follow-up, the percentage of patients with adequate relief in the intervention group was 26.2%, as compared to 13.7% in the control group (Table 2). Between group differences were not statistically significant in adjusted analysis (Table 4). As for quality of life, patients within the intervention group improved significantly both for PCS and MCS as compared to the control group (Table 2). Quality of life changes between intervention and control group did not differ in adjusted analysis (Table 4). As for the secondary outcomes, patients within the intervention group improved significantly on overall current health, severity of symptoms pain and fatigue, severity of psychosocial symptoms subscale distress, subscale anxiety and subscale somatization, and the illness perception items consequences, personal control and identity (Table 3). Also in the long-

term, no statistically significant within group differences were found in the usual care group. Secondary outcome measures did not differ between intervention and control group in adjusted analysis (Table 4).

Long-term results of the per-protocol analyses showed similar results on the primary outcome measures as the intention-to-treat analyses. Only on the self-efficacy questionnaire subscale "self-monitoring and insight" a statistically significant difference between groups was found (Table 5). The sensitivity analyses demonstrated comparable findings on subjective symptom impact (results not presented).

Table 2. Unadjusted primary outcome measures. Mean (SD) of groups, mean (SD) difference within groups, and mean difference (95% CI) or odds ratio (95% CI) between groups.

Groups						Difference within groups				Difference between groups	
Week 0		3 months		12 months		3 months minus Week 0		12 months minus Week 0		3 months minus Week 0	12 months minus Week 0
Exp (n = 80)	Con (n = 80)	Exp	Con	Exp	Con	Exp	Con	Exp	Con	Exp minus Con	Exp minus Con
Quality of Life RAND-36 (0-100)											
Physical Component Scale											
42.7 (7.3)	42.7 (10.1)	46.5 (13.1)	43.9 (12.8)	46.5 (15.1)	43.9 (14)	3.7 (11.8)	1.3 (9.6)	3.7 (15.1)	1.3 (13.7)	MD 2.5 (-0.7 to 5.7)	MD 2.5 (-1.9 to 6.6)
Mental Component Scale											
41.9 (12.7)	46 (11.6)	46.5 (20.1)	49 (15.2)	46.6 (17.2)	48.1 (14.7)	4.6 (20.2)	3 (14.6)	4.7 (17.4)	2.1 (15.1)	MD -0.3 (-5.5 to 4.8)	MD 0.4 (-4.3 to 5.1)
Impact of symptoms Adequate relief (yes/no)											
Responder, n (%)											
..	..	25 (31.2)	11 (13.7)	21 (26.2)	11 (13.7)	..	..	..	..	OR 2.9 (1.2 to 6.9)	OR 2.1 (0.8 to 5.5)
Non-responder, n (%)											
..	..	55 (68.8)	69 (86.3)	59 (73.8)	69 (86.3)	..	..	..	..		

Exp = experimental group, Con = control group

Table 3. Unadjusted secondary outcome measures.

Outcome	Groups					
	Week 0		3 months		12 months	
	Exp (n = 80)	Con (n = 80)	Exp	Con	Exp	Con
Severity of symptoms NRS (0-10)						
Pain	5.2 (2.4)	4.8 (2.5)	4.2 (5.7)	4.5 (4.1)	3.9 (3.8)	4.5 (3.7)
Fatigue	6.2 (2.6)	5.7 (2.6)	5.2 (5.3)	5.4 (4.1)	5 (2.8)	5.1 (3.4)
Severity of psychosocial symptoms 4DSQ						
Distress (0-32)	13.5 (8.6)	11.2 (8.4)	10.5 (15.8)	9.5 (11.3)	10.4 (10.7)	9.4 (10)
Depression (0-12)	2 (3)	1.3 (2.6)	1.4 (4.6)	1.1 (3.5)	1.3 (4.1)	1 (3.4)
Anxiety (0-24)	3.2 (4.3)	2.4 (4.5)	2.2 (6.5)	2.1 (5.3)	1.8 (4.1)	1.7 (4.3)
Somatization (0-32)	13.4 (6.9)	12 (6.9)	10.4 (11.1)	10.8 (8.4)	9.7 (9.5)	10.4 (9.3)
Physical behaviour (h/d)						
Sedentary behaviour	9 (2.4)	9 (2.2)	9.2 (5.3)	9 (4)	8.6 (3.5)	8.3 (3.4)
Moderate or vigorous physical activity	0.4 (0.5)	0.6 (0.6)	0.6 (1.3)	0.6 (1)	0.4 (0.8)	0.6 (0.9)
EQ VAS (0-100)						
Overall current health	60.7 (19.3)	67.2 (17)	72.2 (38.8)	70.5 (28.6)	69.3 (26.8)	69.6 (24)
Illness perceptions IPQ-k (0-10)						
Consequences	5.8 (2.7)	5.2 (2.7)	5.4 (5.8)	5.2 (4.2)	4.8 (3.6)	4.7 (3.8)
Timeline	7.4 (2.6)	7.5 (3.3)	7.3 (7.1)	7.5 (5.3)	7.3 (4.7)	7 (4.6)
Personal control	4.3 (2.3)	4.6 (2.7)	5.8 (6.4)	5.2 (4.5)	5.7 (4.1)	5.1 (4)
Treatment control	6 (2.2)	4.9 (3)	6.2 (6.8)	5 (4.8)	5.4 (4.6)	5.2 (4.8)
Identity	6.4 (2.1)	6 (2.3)	5.9 (4.5)	5.6 (3.3)	5.2 (3.6)	5.5 (3.6)
Concern	5.7 (2.7)	5 (2.9)	5.1 (6)	4.5 (4.5)	4.8 (4.1)	4.4 (3.6)
Coherence	5.3 (2.2)	5.9 (3.2)	6.8 (5.6)	6.5 (4.2)	6.3 (4.2)	5.9 (4.3)
Emotional response	6.1 (2.7)	5.2 (3.2)	5.2 (6.3)	4.2 (4.3)	5.1 (3.8)	4.3 (4)
Self-efficacy HEI-Q (1-4)						
Health-directed activity	2.94 (0.69)	3.27 (0.64)	3.16 (1.29)	3.29 (0.91)	3.13 (0.88)	3.27 (0.76)
Positive & active engagement in life	2.96 (0.55)	3.05 (0.55)	3.05 (0.97)	3.08 (0.70)	3.09 (0.84)	3.04 (0.77)
Self-monitoring & insight	2.80 (0.44)	2.93 (0.45)	3.00 (1.09)	2.90 (0.79)	3.03 (0.70)	2.91 (0.73)
Constructive attitude & approaches	3.02 (0.53)	3.13 (0.59)	3.09 (1.05)	3.16 (0.79)	3.15 (0.77)	3.15 (0.69)
Skill & technique acquisition	2.51 (0.54)	2.81 (0.58)	2.90 (1.55)	2.84 (1.06)	2.86 (0.76)	2.85 (0.76)
Social integration & support	2.76 (0.67)	2.86 (0.63)	2.92 (1.31)	2.91 (0.90)	2.83 (0.87)	2.98 (0.93)
Emotional distress	2.87 (0.65)	3.06 (0.63)	3.05 (1.19)	3.14 (0.89)	3.10 (0.95)	3.20 (0.86)
Health service navigation	2.98 (0.53)	2.99 (0.56)	3.04 (1.22)	3.03 (0.94)	3.06 (0.75)	3.07 (0.85)

Exp = experimental group, Con = control group; Mean (SD) of groups, mean (SD) difference >>

Difference within groups				Difference between groups	
3 months minus Week 0		12 months minus Week 0		3 months minus Week 0	12 months minus Week 0
Exp	Con	Exp	Con	Exp minus Con	Exp minus Con
-1 (5.6)	-0.3 (3.9)	-1.3 (4)	-0.3 (3.7)	MD -0.5 (-2 to 0.9)	MD -0.8 (-1.9 to 0.3)
-1.1 (5.4)	-0.3 (4)	-1.2 (4.1)	-0.6 (3.4)	MD -0.5 (-1.9 to 0.9)	MD -0.3 (-1.3 to 0.8)
-3 (15.2)	-1.7 (10.8)	-3.1 (11.5)	-1.8 (10.7)	MD -0.5 (-4.3 to 3.4)	MD 0.1 (-3.1 to 3.2)
-0.6 (4)	-0.2 (2.9)	-0.7 (4.2)	-0.3 (3.7)	MD -0.3 (-1.3 to 0.8)	MD 0 (-1.1 to 1.1)
-1 (6.2)	-0.3 (4.6)	-1.4 (5.3)	-0.7 (5.3)	MD -0.3 (-1.9 to 1.2)	MD -0.1 (-1.3 to 1.1)
-3 (10.3)	-1.2 (7.3)	-3.7 (10.3)	-1.6 (8.6)	MD -1.4 (-4 to 1.2)	MD -1.4 (-3.9 to 1.2)
0.2 (5.7)	0 (4.4)	-0.3 (4.1)	-0.7 (3.8)	MD 0.2 (-1.1 to 1.5)	MD 0.3 (-0.7 to 1.3)
0.1 (1.3)	0 (1)	0 (0.9)	0 (0.9)	MD 0.1 (-0.3 to 0.5)	MD -0.1 (-0.4 to 0.1)
11.4 (39.9)	3.2 (27.4)	8.6 (30.2)	2.4 (25.4)	MD 4.9 (-5.2 to 15)	MD 1.6 (-5.9 to 9.1)
-0.5 (5.9)	-0.1 (4.1)	-1 (3.8)	-0.5 (3.6)	MD -0.1 (-1.6 to 1.4)	MD -0.2 (-1.3 to 0.8)
-0.1 (7)	-0.1 (4.8)	-0.1 (4.9)	-0.6 (4.5)	MD -0.1 (-1.9 to 1.7)	MD 0.4 (-0.9 to 1.7)
1.5 (6.7)	0.6 (4.7)	1.4 (4.6)	0.5 (4.3)	MD 0.6 (-1.1 to 2.3)	MD 0.6 (-0.6 to 1.9)
0.2 (6.8)	0.1 (5)	-0.6 (4.9)	0.3 (5.2)	MD 0.7 (-1 to 2.5)	MD 0 (-1.5 to 1.4)
-0.5 (4.3)	-0.3 (3.2)	-1.2 (3.6)	-0.5 (3.4)	MD 0 (-1.1 to 1.2)	MD -0.5 (-1.5 to 0.5)
-0.6 (6)	-0.5 (4.3)	-0.9 (4.2)	-0.6 (4)	MD 0.2 (-1.4 to 1.8)	MD 0.2 (-0.9 to 1.3)
1.5 (5.9)	0.6 (4.4)	1 (4.6)	0 (4.8)	MD 0.6 (-1 to 2.1)	MD 0.5 (-0.7 to 1.8)
-0.9 (6.2)	-1 (4.2)	-1 (4)	-0.9 (4.4)	MD 0.5 (-1.2 to 2.1)	MD 0.5 (-0.7 to 1.6)
0.23 (1.27)	0.02 (0.87)	0.19 (1.01)	0 (0.91)	MD 0.06 (-0.25 to 0.37)	MD -0.07 (-0.34 to 0.20)
0.09 (0.93)	0.02 (0.64)	0.13 (0.86)	-0.01 (0.77)	MD 0.04 (-0.21 to 0.28)	MD 0.09 (-0.15 to 0.33)
0.21 (1.09)	-0.03 (0.72)	0.23 (0.77)	-0.01 (0.72)	MD 0.19 (-0.09 to 0.47)	MD 0.16 (-0.04 to 0.37)
0.08 (1.01)	0.03 (0.73)	0.13 (0.77)	0.02 (0.73)	MD 0.01 (-0.25 to 0.27)	MD 0.05 (-0.15 to 0.26)
0.39 (1.60)	0.03 (1.09)	0.35 (0.87)	0.04 (0.81)	MD 0.16 (-0.21 to 0.54)	MD 0.21 (-0.11 to 0.35)
0.16 (1.30)	0.05 (0.89)	0.07 (0.94)	0.12 (0.95)	MD 0.07 (-0.26 to 0.39)	MD -0.11 (-0.36 to 0.14)
0.17 (1.16)	0.08 (0.77)	0.23 (1)	0.14 (0.86)	MD 0.04 (-0.25 to 0.32)	MD -0.02 (-0.26 to 0.23)
0.05 (1.15)	0.04 (0.84)	0.08 (0.83)	0.08 (0.87)	MD 0.02 (-0.28 to 0.31)	MD 0 (-0.23 to 0.22)

<< within groups, and mean difference ; (95% CI) or odds ratio (95% CI) between groups.

Table 4. Multivariate comparisons of primary and secondary outcome measures per group based on intention-to-treat analysis at 3 and 12 months.

	Difference between groups	
	3 months minus Week 0	12 months minus Week 0
	Exp minus Con	Exp minus Con
Quality of Life RAND-36 (0-100) *		
Physical Component Scale	2.3 (-1.2 to 5.8)	2.9 (-1.5 to 7.3)
Mental Component Scale	0.3 (-5.1 to 5.7)	0.6 (-4.2 to 5.5)
Impact of symptoms†		
Adequate relief (yes/no)	2.8 (1.1 to 7.3)	2.3 (0.8 to 6.7)
Severity of symptoms NRS (0-10)*		
Pain	-0.7 (-2.3 to 0.8)	-0.9 (-2 to 0.3)
Fatigue	-0.7 (-2.1 to 0.7)	-0.4 (-1.4 to 0.7)
Severity of psychosocial symptoms 4DSQ *		
Distress (0-32)	-0.8 (-4.7 to 3.2)	-0.3 (-3.7 to 3)
Depression (0-12)	-0.3 (-1.4 to 0.8)	-0.2 (-1.4 to 1)
Anxiety (0-24)	-0.3 (-2 to 1.3)	-0.2 (-1.5 to 1.1)
Somatization (0-32)	-1.6 (-4.4 to 1.2)	-1.7 (-4.5 to 1)
Physical behaviour (h/d)*		
Sedentary behaviour	0.4 (-1 to 1.7)	0.3 (-0.7 to 1.4)
Moderate or vigorous physical activity	0.1 (-0.3 to 0.5)	-0.1 (-0.4 to 0.2)
EQ VAS (0-100)*		
Overall current health	5.8 (-4.7 to 16.3)	3.6 (-4.2 to 11.4)
Illness perceptions IPQ-k (0-10)*		
Consequences	-0.1 (-1.7 to 1.6)	-0.3 (-1.5 to 0.8)
Timeline	0 (-1.9 to 1.8)	0.6 (-0.8 to 2)
Treatment control	0.8 (-1.1 to 2.6)	0 (-1.5 to 1.5)
Identity	0.1 (-1.2 to 1.3)	-0.5 (-1.6 to 0.5)
Concern	0.3 (-1.4 to 2)	0.1 (-1.1 to 1.3)
Personal control	0.8 (-1 to 2.7)	0.7 (-0.6 to 2)
Coherence	0.6 (-0.9 to 2.2)	0.4 (-0.9 to 1.7)
Emotional response	0.5 (-1.2 to 2.3)	0.4 (-0.8 to 1.6)

Table 4. Continued

	Difference between groups	
	3 months minus Week 0	12 months minus Week 0
	Exp minus Con	Exp minus Con
Self-efficacy HEI-Q (1-4)*		
Health-directed activity	0.06 (-0.27 to 0.38)	-0.08 (-0.36 to 0.21)
Positive and active engagement in life	0.04 (-0.23 to 0.30)	0.10 (-0.15 to 0.36)
Self-monitoring and insight	0.18 (-0.11 to 0.47)	0.18 (-0.04 to 0.40)
Constructive attitude and approaches	-0.01 (-0.29 to 0.27)	0.06 (-0.16 to 0.28)
Skill and technique acquisition	0.18 (-0.22 to 0.58)	0.15 (-0.09 to 0.39)
Social integration and support	0.07 (-0.28 to 0.42)	-0.12 (-0.37 to 0.13)
Emotional distress	0.01 (-0.29 to 0.31)	0.01 (-0.25 to 0.26)
Health service navigation	0.01 (-0.31 to 0.32)	-0.01 (-0.24 to 0.23)

**Data are differences in mean (95%CI); †Data are odds ratio (95% CI); Exp = experimental group, Con = control group*

Table 5. Primary and secondary outcome measures based on per-protocol analysis at 3 and 12 months.

	Difference between groups	
	3 months minus Week 0	12 months minus Week 0
	Exp minus Con	Exp minus Con
Quality of Life RAND-36 (0-100) *		
Physical Component Scale	3 (0 to 6)	3.1 (-1 to 7.3)
Mental Component Scale	1 (-3.6 to 5.5)	1.4 (-3.4 to 6.3)
Impact of symptoms†		
Adequate relief (yes/no)	2.8 (1 to 8)	2.3 (0.8 to 7)
Severity of symptoms NRS (0-10)*		
Pain	-1 (-2.1 to 0.2)	-1 (-2.1 to 0.2)
Fatigue	-1 (-2.2 to 0.1)	-0.4 (-1.5 to 0.7)
Severity of psychosocial symptoms 4DSQ*		
Distress (0-32)	-1.1 (-4.4 to 2.1)	-0.2 (-3.3 to 2.9)
Depression (0-12)	-0.3 (-1.3 to 0.6)	-0.2 (-1.3 to 1)
Anxiety (0-24)	-0.4 (-1.8 to 1)	-0.1 (-1.4 to 1.2)
Somatization (0-32)	-1.8 (-4 to 0.4)	-1.2 (-3.7 to 1.4)
Physical behaviour (h/d)*		
Sedentary behaviour	0.3 (-0.8 to 1.5)	0.5 (-0.5 to 1.5)
Moderate or vigorous physical activity	0.1 (-0.2 to 0.4)	-0.1 (-0.4 to 0.1)
EQ VAS (0-100)*		
Overall current health	5.8 (-2.3 to 13.8)	5.4 (-2.4 to 13.2)
Illness perceptions IPQ-k (0-10)*		
Consequences	-0.1 (-1.4 to 1.2)	-0.2 (-1.4 to 0.9)
Timeline	0 (-1.5 to 1.4)	0.9 (-0.5 to 2.4)
Personal control	1 (-0.4 to 2.4)	0.6 (-0.6 to 1.8)
Treatment control	1.1 (-0.5 to 2.7)	-0.1 (-1.6 to 1.3)
Identity	-0.3 (-1.3 to 0.6)	-0.7 (-1.8 to 0.3)
Concern	0.2 (-1.2 to 1.6)	0.2 (-1 to 1.4)
Coherence	0.8 (-0.5 to 2.1)	0.4 (-0.9 to 1.7)
Emotional response	0.6 (-0.7 to 1.9)	0.5 (-0.8 to 1.8)

Table 5. Continued

	Difference between groups	
	3 months minus Week 0	12 months minus Week 0
	Exp minus Con	Exp minus Con
Self-efficacy HEI-Q (1-4)*		
Health-directed activity	0.06 (-0.20 to 0.31)	-0.05 (-0.30 to 0.21)
Positive and active engagement in life	0 (-0.21 to 0.21)	0.13 (-0.10 to 0.36)
Self-monitoring and insight	0.22 (0 to 0.45)	0.22 (0.01 to 0.43)
Constructive attitude and approaches	-0.03 (-0.25 to 0.20)	0.09 (-0.14 to 0.30)
Skill and technique acquisition	0.21 (-0.13 to 0.54)	0.18 (-0.06 to 0.41)
Social integration and support	0.05 (-0.23 to 0.32)	-0.14 (-0.40 to 0.13)
Emotional distress	-0.01 (-0.25 to 0.23)	0.01 (-0.26 to 0.27)
Health service navigation	0.01 (-0.24 to 0.27)	-0.01 (-0.23 to 0.22)

**Data are differences in mean (95%CI); †Data are odds ratio (95% CI); Exp = experimental group, Con = control group*

Discussion

This is the first multicenter cluster randomized clinical trial of a proactive, blended and integrated intervention with a physical therapist and mental health nurse for primary care patients with moderate MUPS aiming at prevention of chronicity. The results showed that more patients who were treated by the PARASOL intervention reported adequate short-term relief as compared to the usual care group, but the difference did not sustain in long-term follow-up. Although quality of life improved within the PARASOL group after the intervention, this improvement did not differ from the usual care group. The PARASOL intervention did not have additional beneficial effects on the secondary outcomes, neither in short-term nor in long-term follow-up.

Subjective symptom impact, measured with the adequate relief question, was one of the primary outcome measures because this subjective outcome adequately reflect the perception of symptoms. Better adequate short-term relief was not accompanied by significant improvements on severity of symptom scores. The explanation for this finding might be that the intervention focused on patients' insight, perception of symptoms and

modifiable prognostic risk factors. Thus the main effect of the PARASOL intervention might be diminishing the impact of symptoms on patients by improving coping strategies and perception of symptoms, without having an effect on symptom severity.

The PARASOL intervention is the first intervention integrating face-to-face sessions with a web-based program in patients with moderate MUPS. This so called blended care can encourage self-management. Although self-management skills improved after the intervention, this improvement did not differ from the usual care group. A possible explanation might be that patients had a lack of intrinsic motivation due to the proactive approach of the GP since the presence of motivation is an important aspect for patients' self-management [43]. Therefore, insight in patients' self-management skills should be assessed for personalization of the intervention, to apply the intervention to the right patients.

Although not statistically significant, a positive trend in the between group differences on quality of life in favour of the PARASOL intervention was found. Not achieving the preset sample size might be an important reason why we were not able to demonstrate the effectiveness of the PARASOL intervention. Our finding is in accordance with a systematic review in non-pharmacological interventions for patients with MUPS, but differ with a more recent primary care intervention in patients with MUPS [41,44]. Sitnikova et al. found a significant effect on the physical component of quality of life at the end of the treatment, but this effect did not sustain on long-term. This is remarkable compared to our results, since our results showed a sustained long-term improvement, although not different from the usual care group. The sustained long-term improvement might be due to the fact that the PARASOL intervention focused on adopting and maintaining a behavioural change. Taking into account the sustained long-term improvement on quality of life and the short-term effect on subjective symptom impact, despite the low power, we recommend to optimize the PARASOL intervention.

Strengths and limitations

The strength of this study is that we opted for cluster randomization, in order to keep the effect of the intervention as pure as possible to prevent a contamination effect. The following limitations of the present study need to be taken into account. First, we only included 160 participants while the desired number of participants was 248. Patients were proactively approached by the GP in the first recruitment strategy, where the number of interested patients was lower than expected. Therefore, we added the second and third recruitment strategy, but we still did not achieve our power. This may raise questions regarding the validity of our results. However, given the non-significant differences in a too small sample but a positive trend in difference in endpoints, we

think that significant differences would have been found if the power was achieved. Secondly, we had to deal with high drop-out rates: 18% after three months and 29% after twelve months. Percentages of missing data in our accelerometer data were even higher. The low number of participants and the high drop-out rates might be attributed to a relatively long follow-up period, the number and length of the measurements and the recruitment strategy where patients were proactively approached by the GP and therefore might be less motivated to change. Thirdly, our included patient group is very heterogeneous. Patients with moderate MUPS differ on severity of symptoms, duration of symptoms and might have varying needs. The heterogeneity might have contributed to more outliers and a wide spread between the participants. A final limitation are the established baseline differences between groups on both primary and secondary outcome measures despite randomization, which might have influenced our findings [42]. Overall, the intervention group had a lower score on baseline measurements as compared to the control group. As a consequence, patients in the intervention group had a higher potential to change. Both groups showed improvements over time, participants in the intervention group slightly better than participants in the control group. This might be attributable to the fact that only patients with more severe complaints wanted to participate, after which the symptoms generally improve during the trial, also known as regression to the mean. In addition, in both groups a proportion of the patients might have improved spontaneously [12].

Given the adequate short-term relief and the improvements within the intervention group on short- and long-term, PARASOL has the potential to become a valuable primary care intervention. Although the PARASOL intervention was not more effective than usual care, cost-effectiveness is still unknown. Future research should assess whether the intervention did affect health care costs compared to the control group.

In conclusion, a relatively short multidisciplinary intervention in primary care, integrating face-to-face sessions with a web-based program does improve subjective symptom impact of patients with moderate MUPS on short-term. No additional beneficial effects on the other outcomes were found. The intervention should be optimized and future research should confirm if the intervention is suitable for patients with moderate MUPS in primary care.

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Chapter 7

Patients' perspective on usability of the PARASOL intervention

Based on:

Patients' perspectives on the usability of a blended approach to an integrated intervention for patients with Medically Unexplained Physical Symptoms: a Mixed-Method study

Submitted

Suze A.J. Toonders
Paula E. van Westrienen
Sophie Konings
Marianne E. Nieboer
Cindy Veenhof
Martijn F. Pisters

Abstract

Background

Medically Unexplained Physical Symptoms (MUPS) are physical symptoms such as pain, fatigue and/or dizziness, that persist for more than a few weeks and cannot be explained after adequate medical examination. Treatment to prevent chronicity of symptoms is recommended. A promising approach is firstly identifying patients at risk and subsequently offering a blended care intervention, with a focus on stimulating self-management, while using eHealth as supportive tool. When these interventions match with patient's expectations, its effectiveness grows.

Objective

This study aimed to get more insights into the usability from the patients' perspective and hence can improve future interventions.

Methods

A mixed-method design was adopted, using quantitative and qualitative data. The System Usability Scale (SUS) measured user satisfaction. Through semi-structured interviews more in-depth insights were gained into patients' perspectives on usability. The analysis process was continuous and iterative. Data was synthesised and categorized along different themes. These themes were analysed for a representative sample of low, medium and high SUS groups, all of equal size.

Results

Saturation was reached after interviewing thirteen participants. Four themes emerged from the interviews: motivations and expectations prior to participating in the program, applicability of eCoaching, the role of healthcare professionals and the integrated design of the blended approach.

Conclusions

Successful implementation of integrated blended care interventions from the patients' perspective requires matching treatment to patients' individual situation and motivation. In addition, personalizing the relative frequency of face-to-face appointments and eCoaching is of importance.

Introduction

Medically Unexplained Physical Symptoms (MUPS) are physical symptoms that persist for more than a few weeks and cannot be explained after adequate medical examination [1]. MUPS are a serious concern, since approximately 25-50% of symptoms remain unexplained in primary care [2-3]. Patients with MUPS experience symptoms such as pain, fatigue and/or dizziness [4]. These symptoms often have a major impact on daily life, with a high burden for patients with MUPS[5]. MUPS can be divided into three consecutive stages, ranging from mild and moderate to chronic stages [6]. These stages are based on the frequency of consultations to the General Practitioner (GP), duration of symptoms and experienced physical and/or psychological dysfunction [6]. Existing research on treatment in the chronic stages of MUPS provides valuable insights, with recommended interventions such as cognitive behavioral therapy, exercise therapy and neuroscience education [7]. Treatment to prevent chronicity of symptoms is recommended in order to reduce symptoms and (in)direct costs [8-9]. This is in line with the general trend in healthcare policy, whereby policy nationwide aims to strengthen health programs to prevent diseases and address risk factors [10]. Healthcare is thereby changing its focus from cure and care to behavior and health [11].

In order for programs to succeed in shifting the focus of treatment on behavior and health, these programs require proactive and indicated prevention [12]. A first step is identifying patients at-risk for developing of chronicity [13-14]. Next, literature shows programs or interventions should focus on stimulating patients' self-management [15-16]. eHealth can serve as a supportive tool for both personalization and stimulating self-management [17-18]. eHealth is not only supportive of the usual therapeutic guidance, but also should be a substantial element of the intervention as a whole [19]. This is referred to as blended care, the combination of face-to-face contact with integrated web-based applications [20], or as eCoaching, defined as 'the use of technology during coaching to motivate and stimulate (groups of) people to change attitudes, behaviors, and rituals' [21-22].

When these interventions match with patients' expectations, its effectiveness in reaching sustainable change in patients grows [23]. Besides, more insights into the usability from the patients' perspective can improve these interventions [24-25]. From the patients' perspective, for example, interventions should by easy to use and acceptable. This usability can be measured, and refers to 'the quality of a system with respect to ease of learning, ease of use and user satisfaction' [26].

The objective of this study is to gain more understanding into patients' perspectives on the usability of integrated blended care interventions. In order to do so, this study looks at a recent proactive, multidisciplinary and integrated blended care intervention, which has been developed to prevent chronicity in patients with MUPS in primary care [27-28]. Patients at risk were identified using electronic medical records [29]. ECoaching was used to integrate technology in the intervention. The main goal was to firstly stimulate self-management of patients, and secondly provide patients insights into dealing with their complaints.

Method

Study design and Setting

A mixed-method design was adopted involving quantitative and qualitative data. The quantitative data consists of the System Usability Scale (SUS). Through semi-structured interviews, qualitative data was gathered in order to gain more in depth understanding into the usability from patients' perspectives. The study has been approved by the Medical Ethical Committee of University Medical Center Utrecht (17-391/C).

Participants

Patients who participated in the PARASOL intervention were eligible for inclusion. To be included in the intervention, all patients (18 years or older) had ≥5 consultations with their GP in the past twelve months. Of these consultations, ≥3 were classified within one of the 104 International Classification of Primary Care (ICPC) codes suggestive of MUPS. Patients with medical and/or psychiatric diagnosis were excluded [28]. Only participants in the PARASOL intervention who gave informed consent for this follow-up study were invited. In order to get rich data, stratified purposeful sampling was applied based on the outcome of the System Usability Scale (SUS). Patients with validated SUS scores of <70, 70-80 and >80 were included, representing low, medium and high user satisfaction, respectively [30].

Measurements

Quantitative data consisted of the outcome of the System Usability Scale (SUS). The SUS has a high reliability[30] and consists of ten questions about the user satisfaction of a system, in this case eCoaching. The validated classification on the basis of SUS scores of <70, 70-80 or a score >80 respectively represent low, medium and high user satisfaction [30]. Questions were answered on a numeric rating scale with a score ranging from one to five ("strongly agree" to "strongly disagree"). The SUS was taken at the end of the intervention. Demographic data consisted of age, gender and educational level (basic, intermediate and high). Educational levels were derived from the standard classification

of education from Statistics Netherlands [31]. Qualitative data were collected by ST in a one-to-one semi-structured interview at an agreed location. A second researcher was available in the role of observer (PEvW or SK). The topic list of the interview was based on the theoretic construct of De Bleser et al 2011 [26] and supplemented by determinants of healthcare innovation selected and developed by TNO [32].

Procedure

Quantitative data was collected for the randomized controlled trail PARASOL (Evaluation of a proactive preventive program in patients with medically unexplained physical symptoms, NL57931.041.16) [28]. Demographic data were retrieved through baseline measurements. After three months, upon completion of PARASOL, SUS was gathered. Qualitative data were collected from semi-structured interviews within four weeks after completing the PARASOL intervention to avoid recall bias. Interviews took place in patients' homes or in one of the participating healthcare centres, depending on the preferences of the patient. Before the interview started, procedures regarding sound recording and coding of data were explained, after which permission was requested.

Table 1. Outline of interview guide [26]

Key area	
Performance	Impact of use environment
	Impact of user characteristics
	Ease of manipulation of device
Satisfaction	Physical dimension
	Privacy dimension
	Human interaction
	Self-concept
	Routine
	Sustainability
Acceptability	Acceptance for daily life use
	Willingness to pay for device

PARASOL intervention

PARASOL consists of a 12-week integrated blended care intervention consisting of four face-to-face consultations with the mental health nurse and five physical therapy sessions, supplemented with eCoaching (figure 1). ECoaching consisted of information modules and video's on self-management and educative themes, video's and instructions on prescribed home exercises and assignments to gradually increasing physical activity program. The whole intervention is directed at patients' perception of symptoms, and modifiable prognostic risk factors for chronicity using therapeutic neuroscience education and encouraging self-management as well as an active lifestyle using a cognitive behavioural approach and graded activity. The healthcare professionals were instructed how to treat patients with moderate MUPS during a two-day training. They were instructed about the content of the intervention with presentations on the study population, central sensitization, therapeutic neuroscience education, graded activity, and perpetuating factors. Furthermore, they were instructed on how to integrate eCoaching during the intervention. For instance, to personalize the general themes to patients level and ask patients if they understood the information was given online. All healthcare professionals received a guideline after finishing the training.

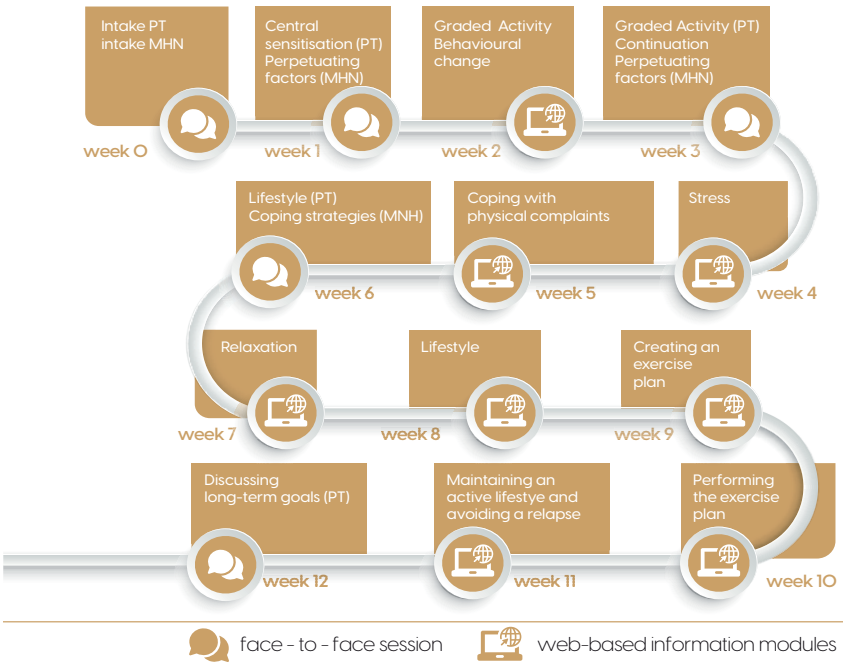

Figure 1. Overview of the PARASOL intervention. *PT, physical therapist; MHN, mental health nurse*

Data analysis

Interviews were recoded and transcribed verbatim and transcriptions were checked by two researchers (ST and SK). Within one week after completing the interview, a summary was sent to all participants. This member check verified whether interpretation was correct. After the first interviews were conducted, the interviewer added other questions based on themes which emerged from previous interviews. Both researchers (ST and SK) encoded meaningful text fragments independently and a set of preliminary concepts and codes were generated. The analysis process was continuous and iterative. Data was synthesised and categorized along different themes. These themes were analysed for low, medium and high SUS groups. The process was supported by an independent expert (MN).

Results

Saturation was reached after thirteen interviews. Interviews lasted for approximately 20-50 minutes, with a mean duration of 33 minutes. Participants had a mean age of 42 years. A majority of participants was female (77%). Five participants had a SUS score of <70, five participants had a score 70-80 and three participants had a score >80. Demographic characteristics of the study population can be found in Table 2.

These interviewees form a subset of participants in the PARASOL intervention (n=80), 71% of whom were female, and with a mean age of 47 years. The overall mean SUS score in the PARASOL intervention (n=55) was 74,6. Twenty participants in the PARASOL intervention did not complete the intervention and five questionnaires were not submitting. A total of 19 participants had a SUS score of <70, fifteen participants had a SUS 70-80 and 21 participants had a SUS above 80 points.

As the use of eCoaching integrated in treatment is relatively new, participants were asked about their general experience and interest in technology in healthcare. Every participant had used some form of technology in the broadest sense of the word. The use of a PC, smartphone and tablet were mentioned. The integration of technology in healthcare as such previously was only experienced by two of the participants. When asked about technology in healthcare, participants mentioned the use of pedometers, health apps and websites. Participants' interest of technology differs, which is shown in table 2.

Table 2. Demographic characteristics

Participant	Age	Gender	Educational level	Previous experience in blended care	Interest in technology in the field of healthcare	SUS score
1	35	Female	Intermediate	No	Yes	67.5
2	48	Female	Intermediate	No	No	60.0
3	38	Female	Intermediate	No	Neutral	77.5
4	23	Female	Intermediate	No	Neutral	57.5
5	42	Female	Basic	No	Neutral	55.0
6	42	Male	Intermediate	No	Yes	50.0
7	48	Female	High	Yes	Yes	77.5
8	43	Female	Intermediate	No	Yes	85.0
9	47	Female	High	Yes	Yes	80.0
10	38	Male	High	No	No	72.5
11	31	Female	High	No	Yes	72.5
12	52	Male	High	No	Yes	87.5
13	57	Female	High	No	No	95.0

Four themes emerged from the interviews, that provide insight into the usability of a blended approach of an integrated intervention from patients' perspectives.

Theme 1

Motivation and expectations prior to participation in the intervention

There was no consensus on participants' expectations prior to the intervention. Some participants stated that they had no expectations or no expectations that the complaints would disappear through the intervention. Others expected less complaints, more physical activity or expected pain to go away. A recurring statement was the hope that someone would seriously look at their complaints. 'That someone finally thinks about the fact that these complaints are really there, and that a program is being made.' (P3). In terms of motivation, some participate mainly for personal interest, other participants just were curious and saw no disadvantages, or started the intervention because of referral from the GP. The amount of suffering was a motivation to participate, and some participants mentioned that there were no other options for treatment for these complaints. 'I take this, because elsewhere a program is never really offered.' (P8). When results are presented based on SUS groups, they show that the higher the SUS

score, the more participants seem to speak in terms of autonomy and intrinsic motivation. For expectations related to this program, there is no difference between SUS groups.

Motivation	
SUS group < 70	'I participate to stay active' 'Advice from GP'
SUS group 70 -80	'Interesting to see whether the mental and physical aspects come together' 'I don't understand my complaints and want to know what they are, and how I can deal with them'
SUS group >80	'I have to make use of this opportunity , as I have been looking for ways to deal with my complaints for two years' 'I had no way to resolve my complaints, and perhaps this will help me'

Expectations	
SUS group < 70	'I don't know if it will work' 'I have no idea what to expect'
SUS group 70 -80	'I'm curious, rather than have any expectations' 'I thought, this must really work'
SUS group >80	'I was open to something new'

Theme 2

Applicability of eCoaching

Twice references were made to eCoaching during interviews. Firstly, concerning the look and feel of the application and secondly, concerning its acceptability. Some participants mentioned they spent a long time searching within the application, and found the online part confusing. 'I had to watch instruction videos but I could not find them.' (P3). Other participants however found the site to be well-structured. There was no consensus on the ease with which documents or instruction videos could be found. Many participants had problems logging in. In addition, the application often had bugs. This did not stimulate the use of eCoaching. 'I did my exercises every day but the program did not work so I just did not fill it in.' (P13). One participant missed an evaluation that would have given insight into progress. The ability to ask questions online and the fact that you can use the intervention anywhere were mentioned as facilitators. Participants stated that the planning assignments and exercises were clear every week. 'What I found very clear was that you could just click and do your exercises and activities on a weekly and daily basis.' (P8). Participants appreciated the possibility to tick off the followed modules, so that it immediately was clear which modules had been completed and which were still open. There was no consensus on whether information through text or film was preferred. Participants gave the following tips for the use of

eCoaching: add forms on the site to leave notes on progress, e.g. how many minutes one walked (P9, P11) and make assignments more accessible by using visual support (colors, shapes) (P7).

The higher the satisfaction measured by the SUS, the more participants understood and used the online environment.

Applicability of eCoaching	
SUS group < 70	'It is unclear for me how to use the website' 'I can't enter the system, I never accessed the online part' 'I often did not fill out the online sections, I prefer face-to-face treatments'
SUS group 70 -80	'I could not find the video, so I used text' 'Clear and easy to use'
SUS group >80	'The videos are clear and easy to use in daily life' 'The site was clear' 'It was easy to get the hang of the application'

Theme 3

The role of healthcare professionals

A much mentioned facilitator in the treatment mentioned in interviews was agreement among healthcare professionals. Participants felt they were receiving the same information from different angles. In face-to-face treatments, which participants felt to be useful, healthcare professionals gave (psycho)education, introducing reminders and repetition to patients. 'Because both the mental health nurse and the physical therapist spoke about interpreting pain, for example, and the physical therapist explains it more anatomically.' (P11). An important role for healthcare professionals was found to be discussing of exercises, giving information, setting goals and helping these goals be reached. Also appreciated by participants was the fact that the healthcare professionals supported reflection on behavior and thoughts by confronting, convincing and motivating. 'Holding up a mirror to me, that there was a confrontation, it was very helpful that the physical therapist was confrontational' (P12). Another facilitator was the approachability of the mental health nurse. Participants recommended more involvement of the GP, for feedback and encouragement. 'I can imagine that people with these complaints do not always immediately think the mental health nurse and the physical therapist are going to solve the problem, so I think that the GP is still important for encouragement.'(P3). Participants did not expect physical therapists to engage in conversations as much as they did. 'I think physical therapy is important only when giving exercises and not for conversations' (P10).

The higher the SUS score, the more patients' understood the role of healthcare professionals as a coach, rather than as a therapist. There is no difference seen between subgroups in relation to inter-professional collaboration.

Role of professionals	
SUS group < 70	'I feel the need to have my own say more' 'Sometimes I feel I have the same conversation twice, the physical therapist and I were a better match and we could converse more easily'
SUS group 70 -80	'The physical therapist remember me and my story, and that made me feel good' 'I expected more from the physical therapist, just conversing and no exercises'
SUS group >80	'The professionals were very involved' 'It's good that the professionals held up a mirror to me'
Inter-professional collaboration	
SUS group < 70	'Good cooperation, same advice' 'The same advices, did not notice cooperation, I did know they coordinated amongst the two of them'
SUS group 70 -80	'The combination of the mental health nurse and the physical therapist was good' 'There was an overlap, but that did not bother me, it was complementary'
SUS group >80	'I know they coordinated, they did not enter each other's domains' 'One was more physical, the other was more psychological'

Theme 4

Integrated design of the blended approach

Given that only two participants had previous experience with blended care, interview questions were asked about this new way of delivering healthcare. Some participants were satisfied with the higher frequency of face-to-face appointments at the start, while others were not. Time between appointments increases the chance of forgetting parts of the treatments. The face-to-face sessions served as a reminder. 'Because I forget a lot, so it's nice that I can have feedback reminder.'(P5). Participants suggested to make the amount of face-to-face sessions dependent on individual preferences. 'I think you should personally consult with each individual on the number of appointments' (P13). Others indicated that the number of face-to-face appointments should be made dependent on one's experience with online applications. 'I think for me personally I could have done with fewer appointments, as I am used to work online.'(P8). Participants mentioned it was important that face-to face sessions and eCoaching are coordinated. 'You are encouraged to do the online program and then you come to practice and

can get the information again, it connects' (P7). The face-to-face sessions fill the gap which was left online. 'In fact, I first had to read the explanation on the website and then my questions were discussed.' (P10). The possibility to schedule the therapy based on personal preferences, was seen as an advantage. 'I liked the times. It was possible for me to make an appointment at the end of the day.' (P7). The advantage of eCoaching was that the participant could prepare specific questions that could be asked during the face-to-face sessions. 'I could ask specific questions I prepared myself.' (P10). Participants generally experience blended care as positive. 'But that you can check it yourself at home. I think this is very good.'(P7).

Participants appreciated the integrated design of the intervention across all the different SUS groups.

Integrated design of the blended approach	
SUS group < 70	'Because feedback is more specific for my own situation' 'Face-to-face was a reminder ... I find personal contact to be very important'
SUS group 70 -80	'The proportion [face-to-face and online] and frequency was good' 'Face-to-face and online matched' 'Repetition made it easier to remember'
SUS group >80	'I find it easy to combine with other activities, I could do with less appointments' 'The number of appointments should be based on personal preferences'

Overall, results of this study show participants experienced the intervention positively. This integrated blended care intervention was aimed at stimulating self-management of patients and secondly, at providing patients with insights into dealing with their complaints. Participants suggested they learned about self-management: 'Now, I can estimate what I can do and cannot do' (P9) and 'I can actually do it all by myself' (P8). Participants also gained more insights into dealing with their complaints: 'Knowing nothing is broken, that idea has reassured me' (P4) and 'Because of graded activity, pain turns into pride; I am happier, undertake more, sing more; I'm enjoying more' (P11).

Table 3 includes all core themes that emerged from the semi-structured interviews, and hence summarizes the usability from patients' perspective, giving factors which were appreciated and giving lessons learned to improve usability.

Table 3. Summary of findings

Patients appreciated:	Lessons learned to improve usability:
• Information being recognizable • The intervention as an incentive • The personal approach • The holistic approach • Inter-professional collaboration	• Connect intervention to individual situation and motivation • Accessibility and tech support of eCoaching • Possibility to ask questions online • Personalize the intervention with respect to the amount of personal guidance alongside eCoaching

Discussion

In this study we evaluated patients' perspectives on the usability of an integrated blended care intervention. All included patients participated in a 12 week proactive blended care intervention in primary care with the aim to prevent chronicity in MUPS. Participants were all generally positive about the received care. Various aspects of usability were highlighted, with responses along four themes.

The first theme which arose from interviews was motivation and expectation of patients prior to the intervention. Literature shows interventions that match with patients' expectations, are more effective in reaching sustainable change in patients grows [23]. This especially goes for intrinsic motivation, rather than extrinsic motivations, increases one's willingness to spend more time on assignments [33] and better healthcare outcomes [34]. Motivation also seems a factor for patients adhering to eHealth [35]. In this study, we find differences in motivation related to satisfaction. The higher the SUS score, the more the participants seem to speak in terms of autonomy and intrinsic motivation. Also here, intrinsic motivation seems to be an important factor related on the experienced usability. Another factor that may influence the patient's motivation is patient selection. Here, an electronic screening method using data from the electronic medical record of the patients' GP was used [29]. All eligible patients at risk for chronicity of complaints were proactively approached by their GP via an invitation letter. The selection of patients through this approach also has implications for patients' motivation, as the chance of approaching patients who may be less motivated may increase. To achieve adherence in patients, one should therefore take motivation into account in future interventions.

Many participants were not satisfied with eCoaching, as technical functions did not work and logging in was a problem. The degree of satisfaction measured with SUS

increases when the online environment is understood and can be used. When patients were uncertain about the usefulness of eCoaching, the eCoaching modules were not used. This is also found in literature. Adapting eHealth to users' understanding and capabilities leads to a more usable and useful system [23]. When looking at the age and educational level of the participants in the lower SUS group, compared to the higher SUS group, a finding that stands out is that the group which is lower satisfied is significantly younger than the satisfaction group. Secondly, those with lower satisfaction have a lower educational level compared to the those who are more satisfied. Literature shows individuals with less education have worse actual and self-rated skills to evaluate the quality of online health information and lower trust in online health information compared to those with more education [36]. Studies however find no consensus regarding the relationship between satisfaction and age [36].

Irrespective of differences in satisfaction with eCoaching, participants were satisfied with the inter-professional collaboration. The holistic approach, in which physical therapists and mental health nurses gave information from different angles was positively received by the participants. Expectations of participants regarding the role of healthcare professionals however differs between the SUS score groups. The higher the SUS score, the more patients' understood the role of the healthcare professionals as coach, rather than as a therapist. Participants in the lower SUS score group for instance felt they had to explain their complaints twice, and expected the role of physical therapist was more than engaging in conversation, and rather giving exercises. As the organization of healthcare has changed, focusing more on prevention [37], the role of healthcare professionals will change, moving from focus from being a therapist the being more of a coach[38]. It seems important to explain this new role at the start of such an intervention, in order to form better expectations of patients. Besides this inter-professional collaboration, also attention should be given to the collaboration between professionals and patients. Shared decision making can support this process [39].

Participants appreciated the integrated design of the intervention across all the different SUS groups. They positively evaluated the possibility of saving text and videos for future reference and repetition of information of eCoaching, combined with face-to-face sessions. Also the ability to personalize face-to-face sessions by allowing patients to prepare specific questions after studying the general information in the eCoaching modules was appreciated. Earlier studies underlined the importance of face-to-face treatment in combination with online care, as this is found to improve and preserve outcomes [35, 36, 42]. The extent to which the intervention was tailored to participants made interventions and information recognizable. A part of the intervention that was mentioned as important, yet missing, was a diary or a free space to take notes on

exercises and days. The option to tick off exercises and modules and the explanation of exercises was considered helpful. This is supported by literature whereby key components for positive effect of eHealth on health outcomes are; personalization, stimulation, goalsetting and integrating of eCoaching [21]. All these elements were available in this integrated blended care intervention.

Strengths and limitations

A limitation in this qualitative study is that all information is based on the specific integrated blended care intervention of PARASOL. Therefore, some items of the core themes are directly linked to the specific intervention. However, recommendations are insightful in general when starting an integrated intervention with a blended approach. Furthermore, the theoretical construct of the Bleser et al was chosen which contains of performance, satisfaction and acceptability [26]. Other theoretical constructs to gather insight into usability also exist, such as the Unified Theory of Acceptance and Use of Technology (UTAUT) and the Technology Acceptance Model (TAM). However, these constructs highly overlap [43-44]. While UTAUT lays more focus on the social influences in relation to behavioural intention, the TAM focuses on the perceived usefulness and ease of use. The strengths of this study are the presence of the iterative process during analysis of the results and the triangulation during the whole research process. Furthermore, patients involvement found place in all research phases.

Conclusions

Successful implementation of integrated blended care interventions from the patients' perspective requires matching treatment to patients' individual situation and motivation. In addition, personalizing the relative frequency of face-to-face appointments and eCoaching is of importance.

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Chapter 8

General discussion

Aim

This thesis aimed to add knowledge on the identification and treatment of patients with moderate MUPS in general practice through evaluation of a new identification method for MUPS based on routine primary care data and evaluation of an integrated, multidisciplinary blended care intervention in a randomized clinical trial in primary care.

Main results

1. We found that patients with moderate MUPS can be adequately identified in general practice registration data with the PRESUME screening method, which supports timely recognition of patients with moderate MUPS by the GP.
2. We demonstrated that patients with moderate MUPS differ from patients with chronic MUPS and from the general population in disease impact: patients with moderate MUPS experience a better quality of life than patients with chronic MUPS, but an inferior quality of life as compared to the general population. Therefore, patients with moderate MUPS can be seen as a clinically relevant group to target in treating MUPS at an early stage.
3. A newly developed blended program integrating physical therapy and a mental health nurse led intervention (PARASOL) is more effective than usual care in relieving symptoms of patients with moderate MUPS at the end of the program. However, the effect was not sustainable: in the long-term after 12 months the outcomes were not different from usual care.
4. We could not demonstrate effectiveness of PARASOL on quality of life, severity of physical and psychosocial symptoms, physical behaviour, illness perceptions and self-efficacy on the short- and long-term.
5. The intervention was well accepted: Participants were generally positive about the holistic and personal approach, inter-professional collaboration and the integrated design of the intervention, despite technical problems and problems with the login of the web-based program.

Putting results into context: interpretation of main findings

The need for timely identification of MUPS

At this moment, Dutch health care policy is focused on transition in health care towards "The right care in the right place" [1]. The essence is prevention of more expensive health care, relocating health care closer to people's homes and substituting health care by other forms such as eHealth. For patients with moderate MUPS this means providing an intervention in primary care and substituting 'on site' health care by eHealth wherever possible. In line with this health care policy, attention should be paid to early identification of patients with moderate MUPS to enable prevention and stimulate self-management. This could prevent chronicity of MUPS and expensive care in the future.

A screening method using routine care data from general practice can effectively support timely early identification. We developed a screening method to identify patients with MUPS called the PRESUME screening method. Based on GP consultation frequency and severity and disease impact without restrictions for the duration of symptoms, patients were identified as having mild, moderate or chronic MUPS. Early identification of patients with MUPS in primary care support a panel management approach. With panel management the focus of care shift from responsive consultation-based care to proactive population-based care [2]. When patients with moderate MUPS are identified early, they can be proactively approached by their GP offering them a preventive intervention.

PRESUME is a prognostic, not a diagnostic method

The PRESUME screening method is not developed to set an accurate diagnosis of MUPS in individual patients. MUPS is hampered by inadequate diagnostic criteria, and is mainly defined by prognosis, i.e. unfavourable disease course characterised by repeated consultations for symptoms that cannot be captured in a physical diagnosis. PRESUME focusses on identifying patients who consulted the GP frequently and in whom did not yet identify the typical MUPS pattern. According to the PRESUME screening method, approximately 50% of the patients with moderate MUPS still experience MUPS symptoms with an impact on patients quality of life after five years. Typical MUPS symptoms are low back pain, fatigue or dizziness. Patients with MUPS have an above average consultation rate, leading to a high burden for GPs due to challenging consultations and difficulties in identifying MUPS. GPs fear to miss a serious medical illness, resulting in further diagnostic investigations and referrals which might lead to iatrogenic harm [3]. The worries of missing a serious medical diagnosis are understandable. However, medically explained diagnoses related to the unexplained symptoms are

rarely found and a medically explained diagnosis is seldom overlooked [4]. Furthermore, diagnostic investigations do not reduce patients' illness concern, health anxiety and symptoms in short-term and long-term [5].

We chose to operationalize mild, moderate and chronic MUPS using the International Classification of Primary Care (ICPC) codes. Patients who consulted the GP with one of the three Functional Somatic Syndromes (chronic fatigue syndrome (A04.01), fibromyalgia (L18.01) and irritable bowel syndrome (D93)) were identified as having chronic MUPS. Patients with mild or moderate MUPS were identified according the presence of ICPC diagnostic codes that referred to MUPS related symptoms without a chronic MUPS diagnosis. Hereby we were able to identify the largest group of patients with MUPS using electronic medical record (EMR) data. These data are sensitive for registration errors. Therefore, GPs should do a validity check to determine if the right patients are selected, to prevent patients being incorrectly proactively approached.

Screening patients with moderate MUPS with routine health care data was time consuming. The three subsequent steps had to be conducted separately. Finally, these results were merged to select the right group of patients. For clinical use, the PRESUME screening method should be implemented into the software of the EMR in current daily practice. When a patient is identified with moderate MUPS the GP should be reminded with an EMR alert. Next, the GP can actively approach the patient with moderate MUPS, offering the patient a preventive intervention.

Developing a multicomponent intervention

Being a complex intervention we used the Medical Research Council (MRC) framework for the development and evaluation of PARASOL [6]. In the development phase, we collected existing evidence. A first step was identifying relevant themes for the intervention. Since a precondition of the intervention was the multidisciplinary aspect, all relevant health care professionals participated in the determination of treatment modalities, i.e. GPs, physical therapists, mental health nurses and health care psychologists. According to the ideas of the health care professionals, eight treatment modalities for a multidisciplinary and blended intervention in patients with moderate MUPS were mentioned as useful treatment modalities. We found an overlap in the determined treatment modalities and already proven effective interventions for patients with chronic MUPS [7-10]. An explanation for this overlap is that health care professionals found treatment modalities in patients with chronic MUPS also applicable for patients with moderate MUPS. This is understandable since both patients with moderate and chronic MUPS experience physical and psychological problems [11]. Despite the overlap on treatment modalities, none of the earlier reported existing interventions in patients

with chronic MUPS integrated a multidisciplinary and blended primary care intervention, nor did the interventions focus on preventing chronicity.

End-user experiences

Previous research pointed out that patients with MUPS are reluctant in accepting the psychological background of MUPS and mental health interventions [12]. Patients perceive it as offensive when their complaints are labelled as "psychological" or by implying that they are "imagining" their symptoms. They experience these labels as stigmatizing, which have a negative impact on the doctor-patient interaction. As the large majority of the MUPS complaints present physically, physical therapy is a more acceptable starting point for an intervention. Therefore, the PARASOL intervention started with an intake session at the physical therapist. After this entry, patients had the intake with the mental health nurse in follow-up. The integration of both disciplines was an important aspect of the PARASOL intervention.

Patients were generally positive about the PARASOL intervention. They described the interaction and collaboration between health care professionals as facilitating. In addition, they mentioned the approachability of the mental health nurse as positive. We were pleasantly surprised by this finding, since this indicates that patients do have an open mind for both physical and psychological aspects. Furthermore, patients appreciated the integration of face-to-face sessions with the web-based program in the PARASOL intervention. The user satisfaction of the web-based program was only moderate, however. Technical problems and problems with the login did not stimulate the use of the web-based program. Furthermore, patients' motivation should be clear prior to the intake session since patients who are intrinsically motivated have better healthcare outcomes and better adherence to eHealth [13,14]. This underlines the importance of blended care, but an improvement on the web-based program and personalization could be made.

MUPS is a dynamic concept, patient population changes over time

A proportion of patients with MUPS will improve spontaneously. When looking at the results of the PRESUME screening method, approximately half to two-thirds of the patients improve after one year and almost one-third of the patients deteriorate, while receiving usual care. Earlier research showed similar results [15,16], and also in our trial we found that in the intervention group 58% of the patients improved and 42% stabilised or deteriorated. In the control group, reverse percentages were seen: 42% improved and 58% remained stable or deteriorated. It is important to note that the treatment results reflect mean within group changes, which does not allow us to make definitive statements on the effectiveness on the PARASOL intervention for individual patients.

Subgroups might benefit more: our results suggest that the PARASOL intervention is more effective in patients with a shorter duration of symptoms, which was also demonstrated in earlier research [12,17]. Of the included patients with a maximum symptom duration of one year, 75% of the patients in the intervention group improved and 25% remained stable or deteriorated. In the control group, 43% improved and 57% remained stable or deteriorated.

PARASOL intervention: successful or not?

On short-term the PARASOL intervention was more effective compared to usual care in symptom relief. On the other outcome measures no statistical differences were found between patients treated with the PARASOL intervention and patients receiving usual care on short- and long-term. Overall, we cannot conclude that the PARASOL intervention is more effective than usual care in patients with moderate MUPS.

The results of the PARASOL intervention are in accordance with a systematic review in non-pharmacological interventions for patients with MUPS, in which summed results did not show benefit in terms of quality of life at the end of the treatment [12]. In contrast to our study, the systematic review reported a significant difference of quality of life at one year follow-up.

Although not statistically significant, the between group differences were in favour of the PARASOL intervention in most outcome measures. Not achieving the preset sample size might be an important reason why we were not able to demonstrate the effectiveness of the PARASOL intervention. On forehand we calculated 248, but only 160 participants were included. In our first recruitment strategy, patients in the routine care database of the GP were screened according to the PRESUME screening method. After a validity check by the GP eligible patients were proactively approached by their GP. Out of 1.583 invited patients, only 130 patients (8%) were included in the trial. Recruitment took much more time and effort than foreseen, which is also known as "Lasagna's law" [18]. Although we added two other recruitment strategies three months after the start of inclusion, we did not reach the required number of participants. As a consequence there was an increased risk of type II error. However, given the non-significant differences in a too small sample but a positive trend in difference in endpoints, we expect that significant differences would have been found if the preset power was achieved. An important side note is that the differences might not reach clinical relevancy.

Different aspects made PARASOL a complex intervention. Key questions in evaluating a complex intervention are: 1. whether the intervention works in clinical practice and 2. which components are active and effective and how are they exerting their

effect [6]. In our opinion, the working aspects of the intervention were the integrated approach by the physical therapist and mental health nurse and the integration of the face-to-face sessions with the web-based program. These aspects were both mentioned as facilitators of the PARASOL intervention according to patients. Taking in account adequate short-term relief, that patients were generally enthusiastic about the PARASOL intervention and that our results may have been better if we had achieved our preset sample size, we believe that the PARASOL intervention deserves optimization and further evaluation.

Optimization of PARASOL

A number of aspects can be optimized. First, the selection of patients and personalization of the PARASOL intervention. Patients were proactively approached and therefore might have a lack of intrinsic motivation [1,19]. Health care professionals confirm that intrinsic motivation of patients is an important aspect in making the intervention successful [20]. Motivation can be achieved through increasing knowledge and better understanding of the behavioural target, but requires awareness of personal beliefs, coping style and intentions [21]. Motivation is also an important condition for self-management. Insight in patients' drives and background is required to personalize the PARASOL intervention, and for applying the intervention to the right patient at the right time. We recommend to assess patients' self-management skills on forehand, to determine how much individual guidance is needed and to create the optimal balance between face-to-face sessions and eHealth.

A second target for improvement is the training of the health care professionals. Blended care is a new way of delivering care, which requires a different way of working for health care professionals. This transformation will be adopted more quickly if the added value of the innovative care is clear. The two day training focused on the content of the PARASOL intervention and the use of the web-based program, with a booster session after six months. During the study period, we experienced some distrust among professionals regarding the use of the web-based program and its integration within face-to-face care. Future training should have more focus on gaining insight in the added value of integrated care and how this supports patients' self-management. Optimization of knowledge, skills and attitude of the health care professionals in delivering a new way of care differ per health care professional. Some health care professionals need more support in this process, while others will learn from experience. We therefore suggest that the intensity and type of training depends on individuals' digital health literacy and motivation towards delivering blended care. A self-test on digital skills can be used to determine how much guidance health care professionals need in order to optimize the usage of eHealth and the integration with face-to-face care [22].

Implementation of PARASOL

Successful implementation of a complex primary care intervention is influenced by a variety of factors [23]. Furthermore, we do know that barriers to implement eHealth include knowledge, time and finances [24].

A lack of knowledge and information about the possibilities and goals, and a limited understanding of benefits can result in a lack of support of stakeholders for the use of eHealth [24]. Furthermore, negative attitudes and beliefs of health care professionals regarding eHealth and lack of time to learn and use eHealth are barriers [23,24]. Health care professionals should understand the "why" of the implementation of eHealth. By our research group, several blended care interventions are already implemented (e-Exercise for patients with osteoarthritis of hip and knee) or currently being studied (i.e., e-Exercise for patients with non-specific low back pain, e-Exercise for patients with neck and/or shoulder complaints and e-Exercise for patients with haemophilia). So far, we can conclude that implementation of these interventions succeeds step by step but it takes time and patience to change daily practice. The provision of training and education to health care professionals is a key success factor.

Concerns about financial consequences are also a barrier, e.g. purchasing and installation costs of eHealth systems and a lack of reimbursement [23,24]. Health care professionals in primary care get paid per session; mental health nurses out of the standard package of health care insurances, physical therapists out of the additional health care insurance. Health care professionals do not get a reimbursement when they perform blended care with probably less face-to-face sessions. Therefore, offering the PARASOL intervention as a healthcare product instead of getting paid per session might facilitate implementation.

During the study period, we already started discussing the implementation of PARASOL. In one of the first meetings, we created a matrix containing needs and perspectives regarding the PARASOL intervention of all individual stakeholders. In two other meetings, potential facilitators and barriers in the implementation of the PARASOL intervention were gained from the perspectives of the physical therapists and mental health nurses. Next, meetings should be organized with GPs, patients with moderate MUPS and healthcare insurance companies to gain insight in their facilitators and barriers. Based on these meetings, an implementation strategy can be developed.

The use of eHealth was not common in daily practice during the study period. In the second quarter of the year 2020, the use of digital technologies in daily practice has increased enormously due to COVID-19. Health care professionals were forced

to provide remote care and gained more experience with the use of eHealth. Of the Dutch general practices, 75% started using more eHealth applications, particularly video consultations [25]. Of those, more than a quarter has the intention to continue video consultations more intensively. Since usability and adherence are prerequisites for an intervention to positively influence health and health behaviour, the lessons learned in the use of eHealth due to the COVID-19 pandemic will facilitate the use of blended care interventions. There are still implementation barriers that need attention, but the belief in the necessity of eHealth has become more clear.

Methodological considerations

Study population

A challenge was the heterogeneity of MUPS population and the complex definition of moderate MUPS. In some cases, health care professionals felt that the PARASOL intervention was not suitable, especially for patients suffering from MUPS for a long time. Furthermore, ambiguity of the definition of moderate MUPS was noticed between the participants in the focus groups. Health care professionals seem to experience difficulties having in mind which patients can be identified as patients with moderate MUPS. Previous research also recognized this problem in patients with MUPS in general [26]. This emphasizes the importance of attention for this patient population in daily practice.

Design

The PARASOL intervention is a complex intervention due to the variability in the MUPS population and the proactive, preventive and blended care. A cluster RCT was chosen to evaluate this complex intervention. This study design allowed us to investigate the effectiveness of the intervention compared to usual care. However, RCT's do have challenges in the evaluation of complex interventions, such as the treatment fidelity, the collaboration of patients and professionals and the risk of bias. Starting with an alternative design would probably have been better, for example a n-of-1 design. A n-of-1 design can describe patterns of behaviour over time and identify individual response to interventions [27]. A type of the n-of-1 design is multiple baseline design. By applying multiple baselines of varying length, observed effects of the intervention can be distinguished from effects due to change. Furthermore, long-term maintenance of behaviour change can be checked by collecting follow-up measurements after the completion of the intervention [27]. With a n-of-1 design an optimal selection and intervention for patients with moderate MUPS could have been achieve [6]. Next, a cluster RCT could have been conducted.

Clinical implication; stepped MUPS care

The current trend in daily practice is a stepped care strategy with attention to self-management. This includes that patients are treated in accordance with their symptom severity by the right professional in the right place at the right time. Patients with MUPS normally consult the GP first. Mild MUPS usually recovers spontaneously. When a patient is identified as having moderate MUPS, the GP could refer her to the PARASOL intervention instead of a separate intervention at the physical therapist or mental health nurse. Nowadays, health care insurance companies require that patients follow a primary care intervention first before they can be referred to secondary care. To our opinion, the PARASOL intervention suits in this requirement. In case of deterioration of symptoms or unsatisfying results, patients could be referred to secondary care.

Implications for future research

Based on our project, several suggestions for future research can be made. Our randomized clinical trial pointed out a positive trend with sustainability on long-term after following the PARASOL intervention, but long-term effects were not statistically significant. Although the PARASOL intervention was not more effective than usual care, cost-effectiveness is still unknown. Healthcare-related costs and indirect (work-related) costs for patients with chronic MUPS are among the highest as compared to patients with specific diseases [28]. Therefore, from a health and an economic view, future research should assess whether the intervention did affect health care costs compared to the control group.

Whereas this thesis focused on patients with moderate MUPS in general, patients with MUPS are heterogeneous. Therefore, effectiveness of the PARASOL intervention may improve by personalization. A key element in the PARASOL intervention was encouraging self-management. Although the potential of this element in an intervention, the level of patients self-management skills differ. It is hypothesized that tailoring the PARASOL intervention to subgroups of patients with high self-management skills and low self-management skills could result in better personalized health care and more effective interventions. Future research should assess this hypothesis.

Finally

In this thesis, a first step has been taken towards early identification and proactive and preventive care in patients with moderate MUPS. Before the PRESUME screening method and the PARASOL intervention can be implemented in clinical practice, optimization is needed. This innovative and integrated care hopefully contributes to prevent chronicity and associated high burdens for patients, health care professionals and society in the future.

Personal note from the author

I started to study MUPS six years ago with the aim that in the future patients with moderate MUPS will receive the right care in the right place at the right time. Early identification of patients with moderate MUPS and a proactive and preventive intervention like PARASOL can contribute to a better policy in treating MUPS. In my work as a physical therapist at Leidsche Rijn Julius Health Care Centers and my work as a lecturer at Fontys University of Applied Sciences, I experienced that MUPS is not a popular topic. MUPS seems to have something elusive upon which people cannot get grip. In clinical practice I noticed that many GPs feel frustrated and irritated by patients with MUPS. They felt relieved when they could refer a patient to me or one of my colleagues of the physical therapy 'chronic pain and unexplained symptoms' expert team. In my work as a lecturer it was clear that students do find MUPS a difficult topic to study. Only a limited number of students were intersted in our project proposals for graduation projects. My mission is to enthuse (future) health care professionals about MUPS with my knowledge and experience through lectures and workshops combined with the implementation of the PRESUME screening method and the optimized PARASOL intervention to support (future) health care professionals in getting more grip on patients with MUPS.

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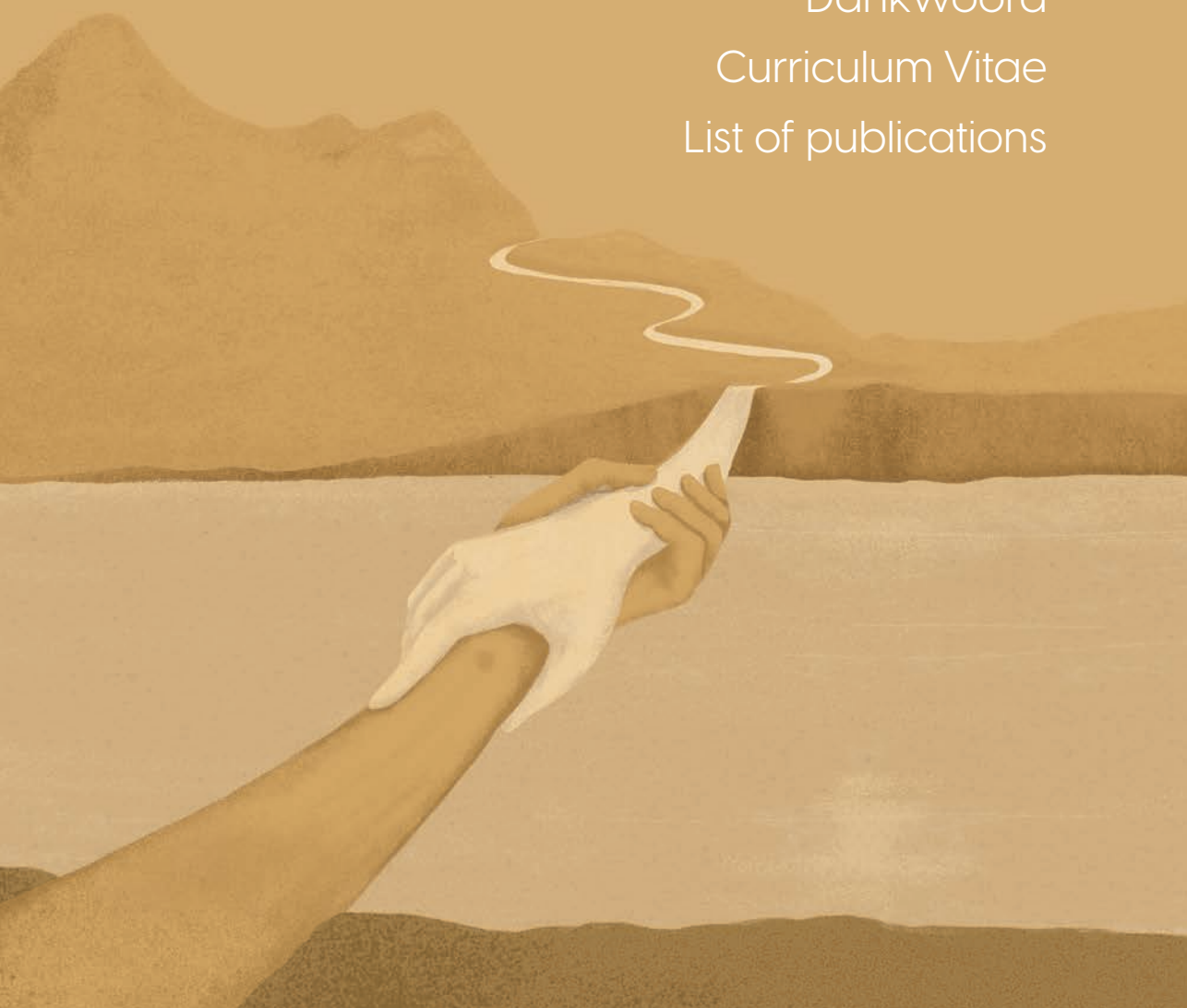
Chapter 9

Appendix



Summary

Everybody can experience physical symptoms. Most people have already Googled their symptoms before consulting a health care professional, since the use of digital technologies is a part of daily life. As described in Chapter 1, these physical symptoms are mostly temporary, remain unexplained and are so called "Medically Unexplained Physical Symptoms" (MUPS). MUPS is defined as physical complaints that last for at least a few weeks and are not explained by a medical condition after proper medical examination. MUPS can be regarded as a continuum with a spectrum from mild, to moderate, and persisting or chronic MUPS. This thesis focused on patients with moderate MUPS to prevent chronicity.

Panel management is a combination of risk assessment followed by a proactive and preventive intervention. With panel management the focus of care shifts from patients who consult the GP with their health problem (responsive consultation-based care) to the GP proactively approach patients at risk of disease, whether or not these patients seek care (proactive population-based care). Patients with moderate MUPS can be identified using routine primary care data. Afterwards, these patients can be proactively approached by their GP, offering them an intervention program directed at prevention of chronicity.

The first step described in Chapter 2 was to determine the prognostic accuracy for identification of moderate MUPS patients using the PRESUME screening method. The PRESUME screening method consists of three subsequent steps: 1) Patients needed to be 18 years or older with at least five general practice consultations in the past twelve months. 2) Patients should not have had a medical and/or psychiatric diagnosis (i.e. chronic obstructive pulmonary disease, hypertension or diabetes mellitus; schizophrenia, anxiety disorder or depressive disorder). 3) Patients were included in one of the three MUPS subgroups based on the presence of MUPS related symptoms. In a random sample of 11.419 patients of the Julius General Practitioners Network, we identified patients with an increased risk of MUPS (mild, moderate, and chronic) using historical data from electronic medical records of general practitioners, and followed them up over a period of 5 years. To determine the prognostic value of the PRESUME screening method in predicting an increased risk of sustained MUPS diagnosis, positive and negative predictive values, and odds ratios were calculated after one and 5 years follow-up. In the index year (2008), 789 patients (6.9% of the patient population) were identified as having mild (n=455; 4%), moderate (n=273; 2.4%) or chronic MUPS (n=61; 0.5%). On average 55.5% of the moderate MUPS patients in 2008, still had MUPS related symptoms or developed chronic MUPS in 5 year follow-up. The positive predictive

value (PPV) for still having MUPS after 1 year follow-up was 67%. The negative predictive value (NPV) was 82.5% after 1 year. After 5 years, the PPV was 48.7% and the NPV was 77.8%. Patients identified with moderate MUPS have 9.8 times higher odds of maintaining MUPS related symptoms or worsening in 1 year follow-up compared to patients with non MUPS. After 5 years follow-up, the odds for sustained MUPS related symptoms or progression to chronic MUPS was 3.3 times higher for patients identified at increased risk of moderate MUPS compared to patients with non MUPS in the index year. Overall, the PRESUME screening method demonstrated moderate prognostic accuracy for sustained MUPS related symptoms after 1 year and low to moderate accuracy after 5 years. The PRESUME screening method can support timely pattern recognition by the GP. After the identification of patients with moderate MUPS, the GP should perform a validity check to ensure that the right patients are selected, to prevent patients being incorrectly proactively approached.

Chapter 3 outlines the identification of treatment modalities based on expert opinions for the development of a multidisciplinary and blended intervention for patients with moderate MUPS to prevent chronicity. A qualitative study with a heterogenic group of professional experts (general practitioners, physical therapists, psychologists, and mental health nurses) was performed. Two focus groups structured using the nominal group technique were carried out. Preconditions were that the intervention is multidisciplinary and blended, with the focus on self-management. A total of 70 ideas were generated from two nominal group meetings. All ideas from both focus groups were ordered according to the scores of the participants and were sorted into eight separate themes with definitions, composed by the principal researcher. The most important treatment modalities for a multidisciplinary and blended intervention in patients with moderate MUPS were (1) coaching to a healthier lifestyle, (2) education regarding psychosocial factors, (3) therapeutic neuroscience education, (4) multidisciplinary intake, (5) multidisciplinary cooperation and coordination, (6) relaxation or body awareness exercises, (7) clear communication by professionals to the patient, and (8) graded activity. These themes provide a first step in developing an intervention for patients with moderate MUPS.

Chapter 4 presents the protocol of a prospective, multicenter cluster randomized clinical trial in the (cost-)effectiveness of a proactive, blended, multidisciplinary intervention (PARASOL) compared to usual care for patients with moderate MUPS. Cluster randomization was performed on health care level to avoid professionals within one health care center offering both the PARASOL intervention and usual care. The PARASOL intervention is a 12-week blended primary care program consisting of 4 face-to-face consultations with the mental health nurse and 5 physical therapy

sessions, supplemented with a web-based program. The aim was to include 248 patients with moderate MUPS (124 patients per arm). Primary outcomes were subjective symptom impact, as registered with the adequate relief question, and quality of life. Secondary outcomes were severity of physical and psychosocial symptoms, general health, physical behaviour, illness perceptions, self-efficacy, and cost-effectiveness. All measurements were performed at baseline, 3, and 12 months after baseline. Retrospective cost questionnaires were also sent at 6 and 9 months after baseline and used for the cost-effectiveness analysis.

In Chapter 5 the characteristics of patients with moderate MUPS were assessed in a cross-sectional study. Baseline characteristics of participants in the PARASOL study were compared to characteristics seen in patients with chronic MUPS and the general population. Furthermore, determinants of the physical and mental components of quality of life assessed with the RAND-36 in patients with moderate MUPS were identified. We found statistical significant and clinical relevant differences in the quality of life between the three groups. Patients with moderate MUPS experience a better quality of life than patients with chronic MUPS but a worse quality of life as compared to the general population. Based on their quality of life scores, patients with moderate MUPS could be adequately distinguished from those with chronic MUPS. Factors associated with the physical and mental components of quality of life in patients with moderate MUPS were gender, age, work status, severity of pain and fatigue, the four domains of severity of psychosocial symptoms, the illness perception "concern", and the average hours per day of Moderate or Vigorous Physical Activity. These factors explain 49.1% of the variance in the physical component of quality of life and 62.9% of the variance in the mental component of quality of life.

Chapter 6 describes the effectiveness of the PARASOL intervention compared to usual care in patients with moderate MUPS. In total 160 participants were included, 80 participants originated from health care centers allocated to the intervention group and 80 from health care centers allocated to the control group. On short-term, after completing the intervention, 31.2% of patients reported adequate relief, as compared to 13.7% in the control group. Although quality of life improved within the PARASOL group after the intervention, this improvement did not differ from the usual care group. The PARASOL intervention did not have additional beneficial effects on the secondary outcomes, neither in short-term nor in long-term follow-up. Not achieving the preset sample size might be an important reason why we were not able to demonstrate the effectiveness of the PARASOL intervention. However, given the non-significant differences in a too small sample but a positive trend in difference in endpoints, we think that significant differences would have been found if the preset power was achieved.

Chapter 7 shows patients' perspectives on the usability of the PARASOL intervention. We therefore conducted a mixed-methods study. The System Usability Scale (SUS) measured user satisfaction of the web-based program. Through semi-structured interviews more in-depth insights were gained into patients' perspectives on usability. Of the participants that completed the SUS (n=55), 35% (n=19) experienced low user satisfaction, 27% (n=15) experienced medium user satisfaction and 38% (n=21) experiences high user satisfaction. The 13 analysed interviews revealed that patients appreciated the personal and holistic approach, recognizable information, the intervention as an incentive, and the inter-professional collaboration. Usability could be improved on the accessibility and tech support of the web-based program, the possibility to ask questions online, and tailoring the intervention to individual' needs. Overall, patients were generally positive about the PARASOL intervention.

Chapter 8 discusses the implications of our main findings. A first step has been taken towards early identification and proactive and preventive care in patients with moderate MUPS. Before the PRESUME screening method and the PARASOL intervention can be used in clinical practice, optimization is needed. For clinical use of the PRESUME screening method, the GP should be reminded with an alert in the electronic medical record when a patient is identified with moderate MUPS. Next, the GP can actively approach the patient with moderate MUPS to offer the PARASOL intervention. Insight in patients' drives and background is required to personalize the PARASOL intervention. We suggest to determine how much individual guidance is needed and to create the optimal balance between face-to-face sessions and eHealth based on the level of patients' self-management skills. Furthermore, future training of the health care professionals should focus on gaining insight in the added value of integrated care and how this supports patients' self-management. The intensity and type of training depends on individuals' digital health literacy and motivation towards delivering blended care. Future research should confirm if the optimized intervention is suitable for patients with moderate MUPS in primary care.

Nederlandse samenvatting

Iedereen ervaart wel eens lichamelijke klachten. Met het dagelijks gebruik van digitale technologieën hebben de meeste mensen hun klachten al gegoogeld voordat ze een zorgprofessional bezoeken. Vaak zijn deze klachten van korte duur en onvoldoende verklaard. Hoofdstuk 1 van dit proefschrift beschrijft de zogenaamde "Somatisch Onvoldoende verklaarde Lichamelijke Klachten" (SOLK). We spreken van SOLK als lichamelijke klachten langer dan enkele weken duren en wanneer er bij adequaat medisch onderzoek geen aandoening is gevonden die de klachten voldoende verklaart. SOLK wordt beschouwd als een continuüm met een spectrum van milde tot matige en chronische SOLK. Dit proefschrift focust op patiënten met matige SOLK ter preventie van chronische SOLK.

Panel management is een combinatie van vroegtijdige identificatie van mensen om hen een proactieve en preventieve interventie aan te bieden. Het verschuift de focus van responsieve zorg (zorg aan patiënten die de huisarts consulteren met een gezondheidsprobleem) naar proactieve zorg (patiënten met een risico op ziekte worden proactief benaderd). Patiënten met matige SOLK kunnen worden geïdentificeerd middels routine data uit het elektronisch patiëntendossier van de huisarts. Na deze identificatie kunnen patiënten proactief benaderd worden door de huisarts om een preventieve behandeling te kunnen volgen.

In hoofdstuk 2 is de prognostische nauwkeurigheid voor het identificeren van patiënten met matige SOLK middels de PRESUME-screeningsmethode onderzocht. De PRESUME-screeningsmethode bestaat uit drie opéénvolgende stappen: 1) Patiënten van achttien jaar of ouder met ten minste vijf consultaties bij de huisarts in de afgelopen twaalf maanden. 2) Patiënten zijn niet gediagnosticeerd met een medische en/of psychiatrische diagnose (d.w.z. COPD, hypertensie of diabetes mellitus; schizofrenie, angststoornis of depressieve stoornis). 3) Patiënten werden geïncludeerd in één van de drie SOLK-subgroepen aan de hand van de aanwezigheid van SOLK gerelateerde symptomen. In een willekeurige steekproef van 11.419 patiënten van het Julius Huisartsen Netwerk werden patiënten met een verhoogd risico op SOLK (mild, matig en chronisch) geïdentificeerd met historische data uit het elektronisch patiëntendossier bij de huisarts. Deze patiënten werden over een periode van vijf jaar gevolgd. Om de prognostische waarde van de PRESUME- screeningsmethode in het voorspellen van een verhoogd risico op een aanhoudende SOLK-diagnose te bepalen, werden positief en negatief voorspellende waarden en odds ratio's berekend na één jaar en na vijf jaar. In het indexjaar (2008), werden 789 patiënten (6.9% van de patiëntpopulatie) geïdentificeerd met milde SOLK (n=455; 4%), matige SOLK (n=273; 2.4%) of chronische

SOLK (n=61; 0.5%). Van de patiënten met matige SOLK uit 2008 bleek na vijf jaar 55.5% nog steeds SOLK gerelateerde klachten te hebben dan wel een was er chronisch SOLK syndroom gediagnosticeerd. De positief voorspellende waarde (PVW) en de negatief voorspellende waarde (NVW) voor het persisteren van SOLK na één jaar was respectievelijk 67% en 82.5%. Na vijf jaar was de PVW 48.7% en de NVW 77.8%. De odds op het houden van SOLK gerelateerde klachten dan wel een verergering van klachten na één jaar is voor patiënten met matige SOLK 9.8 keer zo groot in vergelijking met patiënten zonder SOLK. Na vijf jaar is de odds op het persisteren dan wel verergeren van SOLK gerelateerde klachten 3.3 keer zo groot voor patiënten met matige SOLK in vergelijking met patiënten zonder SOLK. In het algemeen heeft de PRESUME-screeningsmethode een matige prognostische nauwkeurigheid voor aanhoudende SOLK gerelateerde klachten na één jaar en een lage tot matige nauwkeurigheid na vijf jaar. Concluderend kan gesteld worden dat de PRESUME-screeningsmethode vroegsignalering door de huisarts kan ondersteunen. Na de identificatie van patiënten met matige SOLK wordt geadviseerd dat de huisarts een validiteitscheck uitvoert om te beoordelen of de juiste patiënten geselecteerd werden, om te voorkomen dat patiënten ten onrechte proactief benaderd werden.

Hoofdstuk 3 schetst de identificatie van onderdelen van een multidisciplinaire en blended behandeling voor patiënten met matige SOLK ter preventie van chroniciteit. Een kwalitatieve studie middels de nominale groep techniek met twee heterogene focusgroepen (huisartsen, fysiotherapeuten, psychologen en POH's-GGZ) vond plaats. Voorafgaand werd besproken dat de interventie multidisciplinair en blended is, met de focus op zelfmanagement. In totaal werden er 70 ideeën gegenereerd. De ideeën van beide groepen werden geordend aan de hand van de scores van de experts. De onderzoeker voegde deze ideeën samen tot acht thema's met definities. Als meest belangrijke behandelonderdelen van een multidisciplinaire en blended behandeling voor patiënten met matige SOLK werden in oplopende volgorde genoemd: (1) coaching naar een gezondere leefstijl, (2) educatie over instandhoudende factoren, (3) educatie over centrale sensitisatie, (4) multidisciplinaire intake, (5) multidisciplinaire samenwerking en coördinatie, (6) ontspanningsoefeningen of lichaamsbewustzijnsoefeningen, (7) heldere communicatie tussen professionals en de patiënt en (8) graded activity.

Hoofdstuk 4 presenteert het studieprotocol van een prospectieve, multicenter cluster gerandomiseerde klinische trial in de (kosten-)effectiviteit naar een proactieve, blended en multidisciplinaire behandeling (PARASOL) vergeleken met gebruikelijke zorg voor patiënten met matige SOLK. Cluster randomisatie werd gedaan op het niveau van de verschillende gezondheidscentra om te voorkomen dat zorgprofessionals binnen één centrum zowel de PARASOL-behandeling als gebruikelijke zorg zouden aanbieden.

De PARASOL-behandeling is een 12-weken-blended eerstelijnsbehandeling met vier face-to-face sessies bij de POH-GGZ en vijf face-to-face sessies met de fysiotherapeut, geïntegreerd met een web-gebaseerd programma. Het doel was om 248 patiënten met matige SOLK (124 per arm) te includeren. Primaire uitkomstmaten waren adequate klachtenverlichting en kwaliteit van leven. Secundaire uitkomstmaten waren ernst van (psychosociale) symptomen, algemeen ervaren gezondheid, beweeggedrag, ziekteperceptie, zelfeffectiviteit en kosteneffectiviteit. Metingen werden uitgevoerd op baseline, na drie maanden en na twaalf maanden. Daarnaast werden kostenvragenlijsten, waarin gevraagd werd naar uitgaven, ziekteverzuim en productiviteitsverlies gerelateerd aan klachten verstuurd aan patiënten na zes en negen maanden.

In hoofdstuk 5 werden de karakteristieken van patiënten met matige SOLK onderzocht in een cross-sectionele studie. Baselinekarakteristieken van patiënten van de PARASOL-studie werden vergeleken met karakteristieken van patiënten met chronische SOLK en met de algemene populatie. Daarnaast werden determinanten van de fysieke en mentale componenten van kwaliteit van leven onderzocht voor patiënten met matige SOLK. Statistisch significant en klinisch relevante verschillen in kwaliteit van leven werden gevonden tussen de drie groepen. Patiënten met matige SOLK ervaren een betere kwaliteit van leven dan patiënten met chronische SOLK, maar een slechtere kwaliteit van leven in vergelijking met de algemene populatie. Gebaseerd op de ervaren kwaliteit van leven kunnen patiënten met matige SOLK adequaat onderscheiden worden van patiënten met chronische SOLK. Factoren die geassocieerd werden met de fysieke componenten zijn: werkstatus, ernst van pijn en vermoeidheid, ernst van de psychosociale klachten (distress en somatisatie), ziekteperceptie (item "bezorgdheid") en het gemiddelde aantal uur per dag van matig tot zwaar intensief lichamelijke activiteit. Factoren die geassocieerd werden met de mentale componenten zijn geslacht, leeftijd, werkstatus, ernst van vermoeidheid, ernst van de psychosociale klachten (distress, depressie, angst en somatisatie), ziekteperceptie (item "bezorgdheid") en het gemiddelde aantal uur per dag van matige tot zwaar intensief lichamelijke activiteit. De totale variantie in de fysieke en mentale component van kwaliteit van leven wordt voor respectievelijk 49.1% en 62.9% verklaard door deze factoren.

Hoofdstuk 6 beschrijft de effectiviteit van de PARASOL-interventie in vergelijking met gebruikelijke zorg bij patiënten met matige SOLK. In totaal werden er 160 participanten geïncludeerd binnen veertien deelnemende gezondheidscentra. Tachtig deelnemers waren afkomstig van gezondheidscentra die waren toegewezen aan de interventiegroep en 80 deelnemers waren afkomstig van gezondheidscentra die waren toegewezen aan de controlegroep. Op korte termijn, aan het einde van

de behandeling, had 31.2% van de deelnemers een positief resultaat op de primaire uitkomstmaat "adequate klachtenverlichting" ten opzichte van 13.7% van de deelnemers in de controle groep. Hoewel de kwaliteit van leven na de interventie binnen de PARASOL-groep verbeterde, verschilde deze verbetering niet van de controle groep. Daarnaast had de PARASOL-interventie geen effect op de secundaire uitkomstmaten, op korte en lange termijn. Een belangrijke reden voor het niet aantonen van een effect is de te kleine steekproef. Echter gezien de positieve trend op korte en lange termijn ten gunste van de PARASOL-interventie, is de verwachting dat significante verschillen waren gevonden als we het benodigde aantal deelnemers hadden bereikt.

Hoofdstuk 7 toont de resultaten van een mixed-methods-studie waarbij het doel was om meer inzicht te krijgen in de gebruiksvriendelijkheid van de PARASOL-behandeling vanuit patiëntenperspectief. De gebruikerstevredenheid van het web-gebaseerde programma werd gemeten met de "System Usability Scale" (SUS). Van de deelnemers die de SUS hebben ingevuld (n=55), ervaarde 35% (n=19) een lage gebruiksvriendelijkheid, 27% (n=15) een gemiddelde gebruiksvriendelijkheid en 38% (n=21) ervaarde een hoge gebruiksvriendelijkheid. In totaal werden dertien patiënten die de PARASOL-behandeling hebben gevolgd geïnterviewd, waarna saturatie was bereikt. De patiënten waardeerden de persoonlijke en holistische benadering, de herkenbare informatie en de interprofessionele samenwerking en zagen de interventie als stimulans. De gebruiksvriendelijkheid kan worden verbeterd ten aanzien van de toegankelijkheid en de technische ondersteuning van het web-gebaseerde programma, de mogelijkheid voor het stellen van online vragen en de afstemming van de behandeling op iemands persoonlijke behoeften. Over het geheel gezien waren de patiënten positief over de PARASOL-interventie.

In hoofdstuk 8 worden de implicaties van onze bevindingen voor de klinische praktijk en voor toekomstig onderzoek bediscussieerd. Een eerste stap is gezet naar vroegtijdige identificatie en proactieve en preventieve zorg bij patiënten met matige SOLK. Optimalisatie is vereist voordat de PRESUME-screeningmethode en de PARASOL-interventie in de dagelijkste praktijk gebruikt kunnen worden. Voor het klinisch gebruik van de PRESUME-screeningsmethode moet de huisarts een waarschuwing krijgen vanuit het elektronisch patiëntendossier als een patiënt geïdentificeerd is met matige SOLK. Vervolgens kan de huisarts de patiënt met matige SOLK proactief benaderen om de PARASOL-interventie aan te bieden. Inzicht in de motivatie en achtergrond van patiënten is nodig om de PARASOL-interventie te personaliseren. Daarnaast moet de optimale balans gecreëerd worden tussen de face-to-face sessies en eHealth aan de hand van het niveau van zelfmanagementvaardigheden van de patiënt. De scholing van zorgprofessionals moet meer gericht zijn op het verkrijgen van inzicht

in de toegevoegde waarde van geïntegreerde zorg en op welke manier dit de zelfmanagement van patiënten ondersteunt. De intensiteit en type scholing hangen af van de digitale vaardigheden en motivatie van individuen om blended zorg te leveren. Toekomstig onderzoek moet bevestigen of de geoptimaliseerde interventie geschikt is voor patiënten met matige SOLK in de eerste lijn.

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Curriculum Vitae

Els van Westrienen was born on April 11, 1989, in Amsterdam, the Netherlands. After graduating from secondary school, she obtained her Bachelor degree in Physiotherapy at Amsterdam University of Applied Sciences in 2011. After graduation, she started working at Vitaalpunt as a physiotherapist were she guided patients with MUPS. Additionally, she started studying Clinical Health Sciences, Physiotherapy Science, at Utrecht University.

After obtaining her Master of Science degree in 2014, she started working as a physiotherapist and researcher at Leidsche Rijn Julius Health Care Centers and the Center for Physiotherapy Research and Innovation in Primary Care. In 2016 she started her PhD study at University Medical Center Utrecht and started working as a lecturer at Fontys University of Applied Sciences. She continued working as a physiotherapist at Leidsche Rijn Julius Health Care Centers.

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