Unexplained Physical Symptoms:

patients' quality of life improved by cognitive-behavioral group treatment tailored to their perspective

Lyonne Zonneveld

Unexplained Physical Symptoms: patients' quality of life improved by cognitive-behavioral group treatment tailored to their perspective

This thesis was printed with the financial support of the Department of Medical Psychology and Psychotherapy of the Erasmus MC, Rotterdam, and the Erasmus University, Rotterdam, the Netherlands.

ISBN	978-94-6190-038-8
Author	Lyonne Zonneveld
Layout by	Chris Bor, Academic Medical Center, Amsterdam, the Netherlands
Printed by	Buijten & Schipperheijn Uitgeverij, Amsterdam, the Netherlands

Onverklaarde Lichamelijke Klachten:
een cognitief-gedragsmatige groepsbehandeling vanuit het patiëntenperspectief verbetert kwaliteit van leven

Unexplained Physical Symptoms:
patients' quality of life improved by cognitive-behavioral group treatment tailored to their perspective

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

prof.dr. H.G. Schmidt

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
woensdag 27 februari 2013 om 15.30 uur

door

Lyonne Noël Lucia Zonneveld
geboren te Reeuwijk

Promotiecommissie

Promotor: Prof.dr. J.J. van Busschbach

Overige leden: Prof.dr. P. Spinhoven
Prof.dr. W.J.G. Hoogendijk
Prof.dr. H.J. Stam

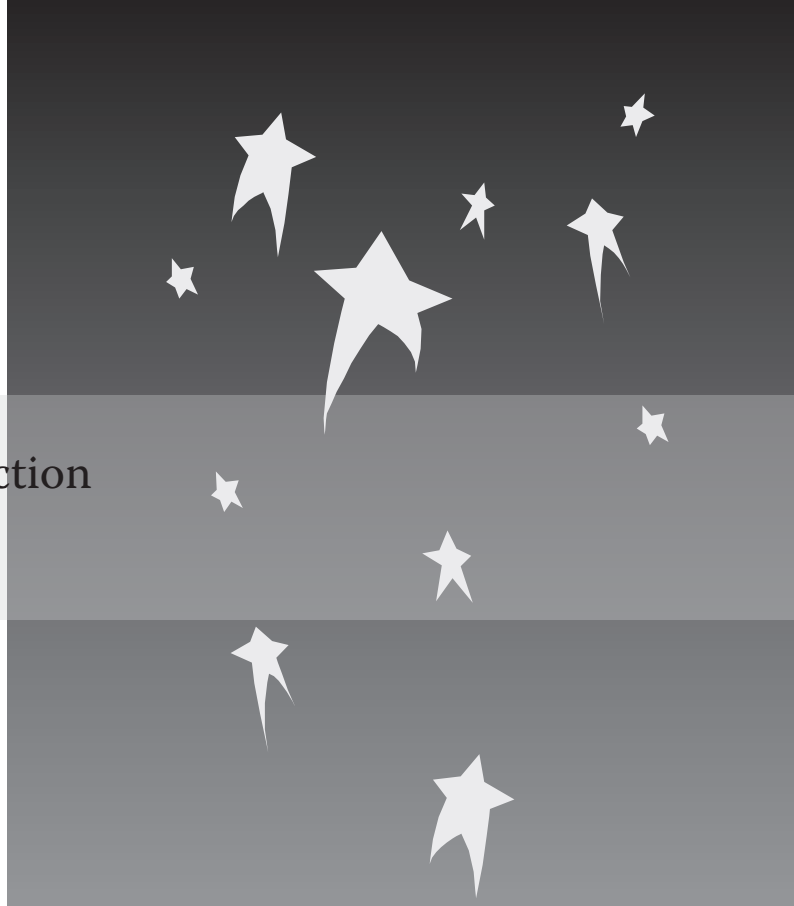
Copromotor: Dr. A. van 't Spijker

Voor hen,
wiens wijsheden mij brachten,
naar waar ik nu ben.

Contents

Chapter 1

General introduction



Introduction

Unexplained Physical Symptoms (UPS) are physical symptoms that cannot be fully explained by a known medical condition. This definition can be refined with supplements such as a minimum number and/or duration of physical symptoms, and/or a certain level of functioning. Depending on these supplements, the estimated prevalence of UPS ranges from 20 to 74% in primary care [85], and from 30 to 52% in secondary care [83; 112; 123; 161].

UPS is more prevalent in women than in men [14; 68; 86; 112; 135; 165] and women in their forties seem to run the highest risk [38; 58; 79; 86; 135]. The comorbidity of DSM-IV Axis I and II disorders in patients with UPS is high: 26 to 58% of patients have a comorbid depressive and/or anxiety disorder [14; 38; 99] and 37 to 88,6% have a comorbid personality disorder [37; 56; 57; 66; 76; 95; 100; 114; 127; 157]. The number of comorbid anxiety and depression disorders in patients with UPS is higher than that in 'comparable', organically explained diseases, for example irritable bowel syndrome versus inflammatory bowel disease or fibromyalgia versus rheumatoid arthritis [67]. The number of comorbid personality disorders in patients with UPS is higher than that in patients with a mood and/or anxiety disorder [56]. Also, the number of comorbid somatic disorders in patients with UPS is significantly higher than that in general primary-care patients [14; 165].

UPS is associated with an impaired quality of life [38; 45; 68; 79]. Having a mental comorbidity makes the prognosis for quality of life even worse [38; 99]. Compared with general primary care patients [38; 58; 79; 99; 165] and with patients with a medical diagnosis [45; 135; 165], patients with UPS report poorer quality of life both in the physical domain and in the mental domain. Compared with primary care patients with a depressive disorder [38; 58; 79; 99], patients with UPS report poorer quality of life in the physical domain, and better quality of life in the mental domain.

Despite the high comorbidity of mental disorders and the impaired quality of life, patients with UPS are more reluctant to accept a psychiatric diagnosis for their symptoms than patients with mental disorders [87]. This might be influenced by patient's perspective on the cause of their symptoms. Compared with patients with a medical diagnosis, patients with UPS attribute their physical symptoms more to physical causes [112], less to lifestyle factors [112] and equally to emotional causes [83; 112]. Patients with UPS visit mostly medical services for their symptoms [14; 87], and their medical utilization is higher than the one found in other patient groups [14; 135].

After consulting a medical service, UPS improves relatively fast in 63 to 76% of the patients [84; 85; 143]. However, UPS persists in 14 to 29% and UPS even becomes worse in 9 to 11% [84; 143]. Absence of improvement after consultation is predicted by a longer duration and a higher number of physical symptoms [84]. The same predictors are also

related to a high number of physician contacts [143]. Patients with UPS who frequently visit the general practitioner evaluate the care of the general practitioner less favorable than patients with other health problems in general or patients with a known medical diagnosis who also frequently visit the general practitioner. General practitioners report not only negative attitudes towards patients with UPS but also insufficient psychological skills to treat them adequately [128].

Cognitive-behavioral therapy has shown to be the most effective treatment for patients with UPS [86; 111; 152]. It reduces UPS and comorbid psychological symptoms, improves daily functioning, and reduces financial expenses without causing harmful effects [65]. However, cognitive-behavioral therapy is reaching only a small group of patients, because it is mostly provided by medical subspecialty clinics or mental health services [4; 86; 122], which are not easily accessible to patients [36], and have a limited treatment capacity. Also, patients generally refuse to be referred to mental health services [5; 122], as most of them are seeing their symptoms in a physical perspective [112; 120].

Aims, research questions and hypotheses

The aims of the study on which this thesis is based were the following:

1. evaluating how quality of life of patients with UPS and societal costs associated with them relate to corresponding data in other patient groups;
2. developing a group training for patients with UPS tailored to their perspective and conducted by secondary community mental health services reaching out into primary care;
3. investigating its effectiveness and the preservation of this effect over a time period of one year;
4. examining whether diagnostics and assessment for this training are useful;
5. evaluating the cost-effectiveness of this training.

These aims resulted in the following research questions and hypotheses:

1.a) What is the quality of life of patients with UPS, and how does it relate to other patient groups?

The study's *hypothesis* was that patients with UPS will have a poor quality of life. Their quality of life was expected to be poorer than that of most other patient groups.

1.b) What are the healthcare-related costs associated with patients with UPS, and how do they relate to corresponding costs in other patient groups?

The study's *hypothesis* was that healthcare-related costs associated with UPS will be high due to high use of medical services. These costs associated with UPS were expected to be higher than those associated with other diseases.

1.c) What are the work-related costs associated with patients with UPS, and how do they relate to corresponding costs in other patient groups?
The study's *hypothesis* was that work-related costs associated with UPS will be high due to absenteeism (absence from work), presenteeism (reduced on-the-job productivity) and paid substitution of domestic tasks. These costs associated with UPS were expected to be higher than those associated with other diseases.

2. Is it possible to develop an easily accessible cognitive-behavioral group training for a large group of patients with UPS that is feasible for a secondary community mental health service reaching out into primary care?
The study's *hypothesis* was that it will be possible to develop an easily accessible cognitive-behavioral group training for a large group of patients with UPS that is feasible for a secondary community mental health service reaching out into primary care.

3.a) Can such a cognitive-behavioral group training effectively improve quality of life of patients with UPS?
The study's *hypothesis* was that the cognitive-behavioral group training will effectively improve patients' quality of life.

3.b) Is patients' improved quality of life preserved in a one-year follow-up period?
The study's *hypothesis* was that patients' improved quality of life will be preserved during the follow-up period.

4. Do variables assessed at baseline and used in routine-practice assessments consistently predict the outcome of the cognitive-behavioral group training, after control for pretreatment scores on the outcome measure and for sociodemographic variables?
In line with clinical practice, the study's *hypothesis* was that better outcome will be predicted by the following: fewer psychological symptoms and personality-disorder characteristics, the absence of a psychiatric history, and a better quality of life in the mental domain.

5. Is the cognitive-behavioral group training cost-effective compared with a waiting list for patients with UPS?
The study's *hypothesis* was that the ratio between costs and effects of the cognitive-behavioral group training will be favorable from a societal perspective using a cost-effectiveness ratio of €30,000 per QALY.

Definition used for Unexplained Physical Symptoms

There is no consensus on the definition of UPS [68]. The definition used for UPS in this study is physical symptoms fulfilling either the DSM-IV criteria of undifferentiated somatoform disorder or those of chronic pain disorder. These DSM-IV criteria include

that the physical symptoms are not intentionally produced of feigned, cause clinically significant distress or impairment in functioning, persist at least six months, and are not better accounted for by other DSM-IV classifications. The clinical relevance of this DSM-IV definition of UPS is indicated by its prognosis and prevalence. Using this refined DSM-IV definition, the prognosis is not favorable [11; 72] and only 25% of the patients with UPS recover after consultation of their general practitioner [11]. Using this refined DSM-IV definition, the prevalence of UPS is 14.6% in general practice [38], which is more than five times the general-practice prevalence of major depressive disorder, more than five times the general-practice prevalence of panic disorder with or without agoraphobia, and more than 18 times the general-practice prevalence of social phobia [38].

Outline of the thesis

This thesis is based on a sequence of articles, which are used as basis for the following chapters.

The **second** chapter of this thesis evaluates the quality of life of patients with UPS and the costs associated with UPS. If patients' quality of life is poor and costs are high, then the need to develop an effective treatment and to investigate the cost-effectiveness of such treatment will be more urgent.

The **third** chapter of this thesis describes the most accepted cognitive-behavioral approach for UPS, the consequences model, and its limitations. The limitations are listed and eliminated by tailoring the consequences model to patients' perspective. The resulting tailored model is the basis of an easily accessible group training. The study design to analyze the effectiveness of the resulting group training is reported in detail.

The **fourth and fifth** chapters of this thesis illustrate how the contents of the group training were experienced by two female patients (in English) and one male patient (in Dutch). The appropriateness of the tailoring to patients' perspective will be reflected in their reactions to the group training.

The **sixth** chapter of this thesis reports on the effectiveness of the group training. If the group training is effective for patients with UPS, then the group training will raise their quality of life, and its effect will be preserved during the one-year follow-up.

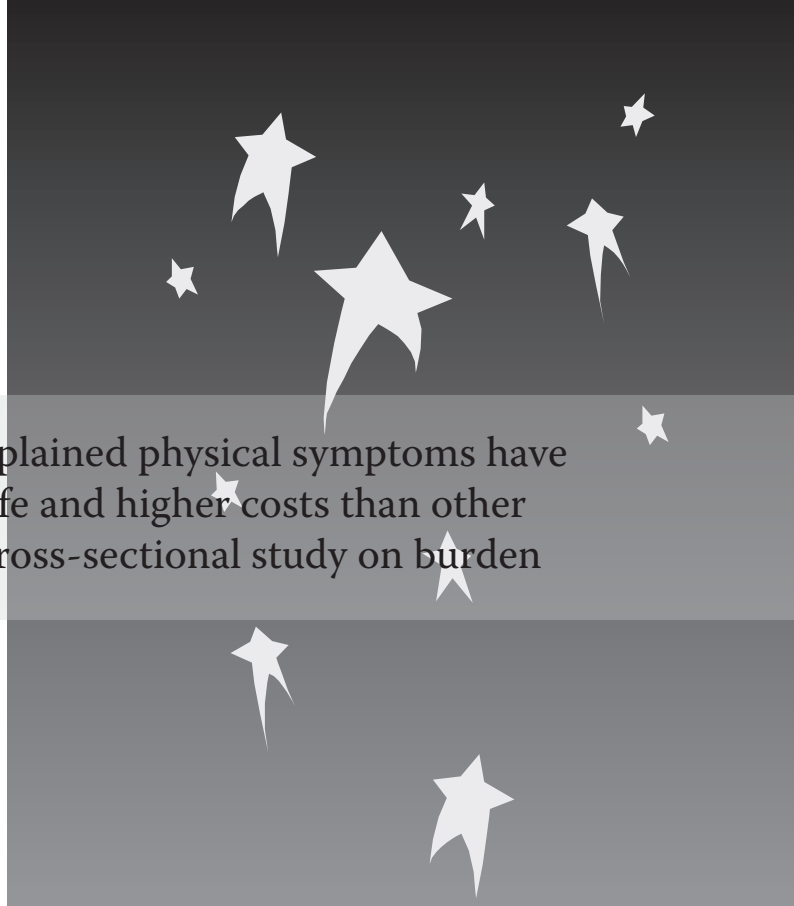
The **seventh** chapter of this thesis shows whether the outcome of the group training might have been predictable on the basis of variables assessed at baseline and used in clinical practice. If the outcome is predictable, then a selection and allocation of patients will further raise the effectiveness. However, if the outcome is not predictable, then a selection and allocation will unnecessarily reduce the accessibility of the treatment.

The **eighth** chapter of this thesis evaluates the cost-effectiveness of the group training. If the ratio between effects and the net investment in this group training (costs subtracted with possible savings elsewhere) is favorable, the group training will be cost-effective. In

that case, implementation and even reimbursement of this group training for UPS will be advisable not only from patients' perspective but also from societal perspective.

The **ninth** chapter of this thesis is the general discussion, which summarizes the main findings, the strengths, and the limitations of this study. By further reflecting on these main findings, clinical and policy implications of the study and the possibilities for future research are presented.

Chapter 2



Patients with unexplained physical symptoms have poorer quality of life and higher costs than other patient groups: a cross-sectional study on burden

Abstract

Background

To determine whether healthcare resources are allocated fairly, it is helpful to have information on the quality of life (QoL) of patients with Unexplained Physical Symptoms (UPS) and on the costs associated with them, and on how these relate to corresponding data in other patient groups. As studies to date have been limited to specific patient populations with UPS, we compared the QoL, healthcare-related costs and work-related costs of a general sample of patients with UPS with those of other patient groups.

Methods

In a cross-sectional study, 162 patients with UPS reported on their QoL, use of healthcare resources and lost productivity in paid and unpaid work. To assess QoL, the generic SF-36 questionnaire was used, from which multidimensional quality-of-life scores and a one-dimensional score (a utility) using the SF-6D scorings algorithm were derived. To assess costs, the TiC-P questionnaire was used.

Results

Patients with UPS reported poor QoL in the physical and social domains, and relatively better QoL in the mental domain. The median of utilities was 0.57. These QoL values were among the poorest of those in all other patient groups.

Healthcare-related costs for patients with UPS were estimated to be over four percent of total Dutch annual healthcare expenditure. They were increased by work-related costs: absence from work (absenteeism), lower on-the-job productivity (presenteeism), and paid substitution of domestic tasks. These costs were among the highest of all patient groups.

The mean total cost per patient per year was estimated to be €6,815.

Conclusions

These findings suggest that patients with UPS have a high burden of disease and use a considerable amount of healthcare resources. This burden for both patients and society helps to justify the allocation of sufficient resources to effective treatment for these patients.

Background

Unexplained Physical Symptoms (UPS), such as chronic fatigue syndrome, are physical symptoms that cannot be explained on the basis of a known medical condition – a definition some studies refine by specifying a minimum number of physical symptoms, a minimum duration of physical symptoms, or a certain level of functioning. Depending on the specific definition and the methods used to classify UPS, the estimated prevalence of UPS ranges from four to 74% in primary care [38; 58; 85], and is 52% in secondary care [83; 112].

As UPS reduces Quality of Life (QoL) [38; 58; 79; 99; 135; 165] and increases costs [14; 124; 135], it is a burden to patients and society alike. These patients' QoL is poor [38; 58; 79; 99; 135; 165]. Overall, it is poorer than in primary care patients [38; 58; 79; 99; 165] and in those with a medical diagnosis [135; 165]. It is harder to determine whether it is also poorer than in patients with conditions such as major depression: though patients with UPS have a poorer QoL in the physical domain, those with major depression have a poorer QoL in the mental domain [38; 58; 79; 99].

To determine whose overall QoL is poorest, the different domains of QoL should be summarized into one-dimensional weighted score. QoL instruments for that purpose summarize overall QoL into a so-called 'utility weight', a value that is usually abbreviated to 'utility' [27; 31]. In a utility, one represents full health and zero is equivalent to death. Although we found three studies that calculated utilities for patients with UPS [58; 104; 118], their generalizability was limited. One study [104] was conducted in a rehabilitation clinic and defined patients with UPS as 'psychosomatic' patients, who were treated for depression, anxiety, and other mental disorders. The second [58] was conducted in primary care and defined UPS as a somatoform disorder, but it excluded the most prevalent somatoform disorder: the undifferentiated somatoform disorder [38]. The third study [118] was conducted in primary care and recruited patients – some of whom were considerably disadvantaged socioeconomically – from general practices in London. To compare patients with UPS with other reference populations, there is a need for more generalizable information on utilities in patients with UPS.

Costs to society are incurred by the healthcare services attended by patients with UPS. One study [135] found $4,700 annual healthcare expenditure per patient; another found $5,678 [14]. Little is known about the less visible societal costs associated with UPS due to lost productivity in paid and unpaid work. For chronic fatigue syndrome, Reynolds et al. [124] estimated that the annual societal costs for lost labor force and household productivity in the United States were $9.1 billion, which amounted to approximately $20,000 per patient [124]. It is unknown whether the cost of chronic fatigue syndrome is representative for the overall group of patients with UPS, or how these costs relate to corresponding costs in reference populations.

Healthcare resources are allocated not only on the basis of effectiveness of the treatment but also partly on the basis of who is 'in greatest need' or has 'the highest burden', as this is considered an egalitarian and thus 'fair' distribution of healthcare resources [149; 150]. Therefore, information is needed on the QoL of patients with UPS, on the costs associated with them, and on how these relate to corresponding data in other patient groups.

Since studies to date have been limited to specific patient populations with UPS, we investigated the following research questions in a general sample of patients with UPS:

1. What is the QoL of patients with UPS, and how does it relate to other patient groups?
2. What are the healthcare-related and work-related costs associated with patients with UPS, and how do they relate to corresponding costs in other patient groups?
3. What is the mean total cost per patient with UPS per year?

Methods

Ethics

The study has been approved by the Erasmus Medical Research Ethics Committee and has been registered in the Dutch Trial Register (NTR 1609) [171]. Patients in this study gave written informed consent.

Study design

This cross-sectional study was part of a randomized controlled trial on the effectiveness of cognitive-behavioral group training for patients with UPS [175]. As part of the baseline measurement, patients were asked to complete self-report questionnaires on QoL and costs. Their outcomes on these questionnaires were compared with those of different reference populations. A more detailed description of the study protocol can be found in Chapter 3 and has been published elsewhere [173].

Study population: patients with UPS

Between February 2005 and September 2008, patients were recruited in general practices, outpatient clinics at general hospitals, and at the Riagg Rijnmond, a secondary community mental health service for the greater Rotterdam area (the Netherlands). General practitioners and specialists were asked to refer patients aged between 18 and 65 years whose physical symptoms, according to their clinical judgment, could not sufficiently be explained on the basis of a known medical condition. Patients were included if they signed the informed consent and if their UPS fulfilled the DSM-IV criteria for an undifferentiated somatoform disorder or a chronic pain disorder. To verify whether UPS fulfilled these DSM-IV criteria, we used the *Structured Clinical Interview*

for DSM-IV Axis I Disorders/Patient edition (SCID-I/P) [55], a semi-structured validated interview for making the major DSM-IV Axis I diagnoses. Patients were excluded if they did not provide informed consent, or if poor language skills or handicaps such as cognitive impairment prevented them from accomplishing the tasks required by the study.

Reference populations

The reference populations were other patient groups and the general population whose QoL or costs had been measured in earlier studies using comparable outcome measures (for further details, see statistical analyses).

Outcome measures

The QoL in different domains was measured using the *36-item Medical Outcomes Study Short-Form General Health Survey* (SF-36) [168], a validated and reliable self-report questionnaire for QoL, designed to be used across a wide range of different populations [1]. The responses to the 36 questions of this questionnaire are converted into eight multi-item subscales: Physical functioning, Role functioning physical, Bodily pain, General health, Vitality, Social functioning, Role functioning emotional, and Mental health. Raw scale scores are linearly transformed into a 0-to-100 scale, a higher score indicating a better QoL.

To extract utilities from the SF-36, a smaller version of the SF-36 has been developed by using eleven SF-36 items to cover six dimensions ('SF-6D'): physical functioning, role limitations, social functioning, pain, mental health, and vitality [25]. Each dimension has between four and six response levels, thereby providing 18,000 possible quality-of-life states. A selection of these states was valued as more or less preferable by a representative sample of the UK general population using a valuation technique called 'standard gamble'. On the basis of their valuations, the utilities for all 18,000 possible health states have been estimated using regression models. As a result, the SF-6D outcomes can now be transformed into a utility, where one represents full health and zero is equivalent to death.

Costs were measured using the 2002 version of the *Trimbos/iMTA Questionnaire for Costs associated with Psychiatric Illness* (TiC-P), a self-report questionnaire for assessing the costs of illness: it has 29 questions and semi-fixed-response alternatives [62]. The first part of the TiC-P measures the healthcare-related costs incurred through the use of healthcare services and medication over the past four weeks. The second part, which is based on the short form of the Health and Labor Questionnaire, measures the work-related costs caused over the past two weeks by absenteeism (absence from work), presenteeism (reduced efficiency at work), and substitution of domestic tasks.

Statistical analyses

First, the SF-36 subscale means of patients with UPS were calculated and compared with those found in earlier studies in patients with major depression, in patients with cancer, and in the general population [1; 89]. According to Osoba [116], the Minimally Important Difference (MID) for SF-36 scores is 10. MID is defined as 'the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management' [73].

Second, the SF-6D median of patients with UPS was calculated and compared with that found in earlier studies in patients with mental disorders and chronic physical conditions and in the general population [52; 81; 82; 155]. According to Walters and Brazier [166], the MID for SF-6D scores is 0.04.

Third, the mean of the healthcare-related costs of patients with UPS was calculated [32; 61; 62]. To compare these health-related costs with the findings of the general Dutch Cost of Illness study [133], the patients' costs had to be expressed as a percentage of total Dutch annual healthcare expenditure. This percentage was compared with the percentages of the main and specific disease categories. For purposes of comparison, we covered the five specific diseases with the lowest annual healthcare expenditures and the five with the highest.

Fourth, the work-related costs of patients with UPS were divided into costs caused by loss of productivity in paid work and costs caused by loss of productivity in unpaid work.

For paid work, patients' mean costs for absenteeism and presenteeism were separately calculated. For the calculation of patients' mean costs for absenteeism, the friction-cost method was used [29; 62]. The friction-cost method assumes that every working person who is absent for 23 weeks and more is replaced by a formerly unemployed person [62] and is therefore excluded from the cost calculations. For absenteeism, the mean number of disability days and the mean percentage of absenteeism in patients with UPS were calculated and compared with those found in earlier studies in the general population, the healthy workforce, and the workforce with chronic illness [63; 74; 78; 137]. The percentage of absenteeism is the number of lost working days due to absenteeism divided by the number of working days according to labor contract and expressed as a percentage. For presenteeism, the mean costs of patients with UPS were calculated and compared with those found in earlier studies in general population and the workforce with chronic illness [24; 63; 137].

For unpaid work, patients' mean costs related to productivity loss in domestic tasks were calculated only if these tasks were substituted by paid professionals [61]. Because the costs found in other studies [134; 137] combined unpaid and paid substitution of domestic tasks, the resulting costs could not be compared with those of different reference populations.

Finally, the mean total of societal costs per patient per year (PPPY) was calculated, which included the costs of healthcare utilization, absenteeism, presenteeism, and paid substitution of domestic tasks.

Results

Patient characteristics

Table 2.1 shows the characteristics of the 162 patients enrolled in the study. Due to missing answers, the SF-6D could not be calculated for five patients (3%).

Table 2.1. Patients' characteristics

Sociodemographic characteristic	**n**	**%**
Gender		
female	131	81%
male	31	19%
Age in years *(mean, SD)*	*45*	*11*
Nationality		
Dutch	141	87%
other	21	13%
Marital status		
married or living with partner	110	68%
unmarried, divorced or widowed	52	32%
Highest education completed		
primary school or less	14	9%
lower vocational or general secondary education	54	33%
intermediate vocational or higher general secondary education	57	35%
higher vocational, pre-university or university education	36	22%
missing	1	1%
Employment		
employed	73	45%
unemployed	89	55%
Number of working hours per week of patients with paid work *(mean, SD)*	*23.9*	*10.9*
Number of working days per week of patients with paid work *(mean, SD)*	*3.9*	*1.2*
Clinical characteristic		
Classification of UPS by SCID-I/P		
undifferentiated somatoform disorder	63	39%
chronic pain disorder	99	61%
Duration of UPS in years *(median, interquartile range)*	*9*	*3-16*

Table 2.1. Patients' characteristics (*continued*)

Number of comorbid DSM-IV Axis I disorders		
no comorbid DSM-IV Axis I disorder	95	59%
one or more comorbid DSM-IV Axis I disorders	67	41%
Number of comorbid DSM-IV Axis II disorders		
no comorbid DSM-IV Axis II disorder	113	70%
one or more comorbid DSM-IV Axis II disorders	47	29%
missings	2	1%
Referrer		
primary medical service	82	51%
secondary medical service	51	31%
secondary mental service	29	18%

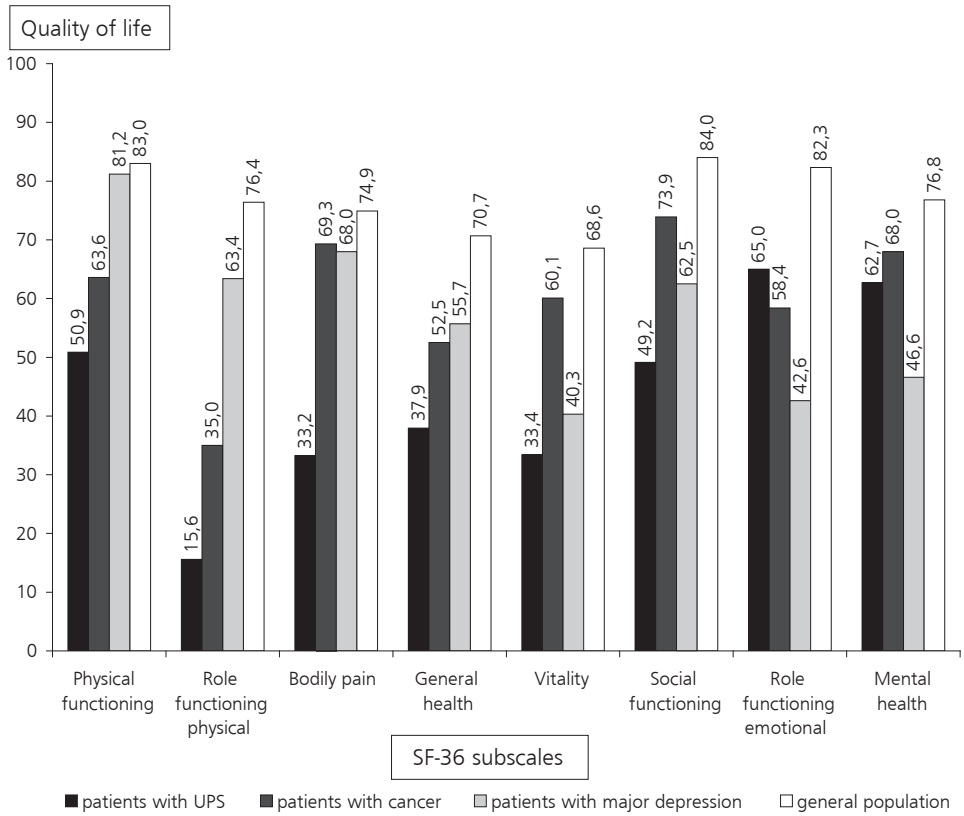


Figure 2.1. Quality of life in different reference populations

Quality of life in different domains

In Figure 2.1, the SF-36 subscale means of patients with UPS were plotted against the means of patients with major depression [89], of patients with cancer [1], and of the

general population [1]. In general, patients with UPS had lower means on the subscales than the reference populations did. However, for each of the three subscales Vitality, Role functioning emotional and Mental health, patients with UPS differed less than the MID from other patient groups. On the 'Vitality' subscale, patients with UPS and those with major depression had comparable means that differed more than the MID from patients with cancer who reported higher vitality. On the 'Role functioning emotional' subscale, patients with UPS and those with cancer had comparable means that differed more than the MID from patients with major depression who reported lower emotional functioning. On the 'Mental health' subscale, patients with UPS and those with cancer

Table 2.2. Utilities in different reference populations

Reference group	N	Utility (median)
General population		
general population [82]	1,005	0.782
Mental disorder		
alcohol dependence or misuse [52]	81	0.737
any substance misuse [52]	122	0.723
specific phobia [52]	232	0.698
generalized anxiety disorder [52]	129	0.681
any anxiety disorder [52]	659	0.660
panic disorder [52]	253	0.606
dysthymia [52]	115	0.603
social phobia [52]	64	0.599
Unexplained Physical Symptoms: UPS	*157*	*0.568*
any mood disorder [52]	476	0.547
major depressive disorder [52]	332	0.527
Chronic physical condition		
heart attack [52]	171	0.755
cancer (breast, lung, colorectal) [155]	184	0.74
diabetes [52]	373	0.738
high blood pressure [52]	1,075	0.737
cardiovascular diseases [52]	496	0.724
chronic pain [52]	2,496	0.723
heart diseases [52]	457	0.723
respiratory conditions [52]	467	0.723
chronic bronchitis [52]	347	0.705
asthma [52]	227	0.705
arthrosis [52]	1,480	0.681
neck pain [52]	1,471	0.675
back pain [52]	1,484	0.669
migraines [52]	717	0.657
Unexplained Physical Symptoms: UPS	*157*	*0.568*

had comparable means that differed more than the MID from patients with major depression who reported lower mental health.

Quality of life summarized in utilities

The utilities in UPS ranged from 0.37 to 0.96; their median was 0.57. In Table 2.2, this median was ranked within that of the general population, those of patients with mental disorders, and those of patients with chronic physical conditions [52; 81; 82; 155]. In general, patients with UPS had a lower utility than the reference populations. The utility of patients with UPS was comparable to that of patients with the following disorders: panic disorder, dysthymia, social phobia, any mood disorder, and cancer. The utility of patients with UPS was more than the MID higher than that of patients with major depression.

Table 2.3. Healthcare visits and healthcare-related costs per patient with UPS per year

Healthcare service	Percentage of patients using the service	Mean visits per patient per year	Mean costs per patient per year in €[1)]	Percentage of total costs
General practitioner	58.64%	15.57	420.31	13.46%
Medical specialist	38.89%	8.43	584.96	18.73%
Physiotherapist	35.80%	14.12	490.25	15.70%
Alternative health practitioner	22.84%	5.22	248.30	7.95%
Company doctor	18.52%	2.97	80.16	2.57%
Secondary community mental health service	11.11%	2.41	396.94	12.71%
Private psychiatric or psychotherapeutic practice	11.11%	2.49	211.08	6.76%
Social worker	9.26%	2.01	125.74	4.03%
Psychiatric outpatient clinic	8.64%	1.12	82.64	2.65%
Self-help group	1.85%	0.32	16.26	0.52%
Inpatient hospital care service	0.62%	0.24	100.98	3.23%
Substance-abuse outpatient care service	0.62%	0.08	2.13	0.07%
Day hospital care service	0.00%	0.00	0.00	0.00%
Medication		**Mean number different medication per patient**		
Medication	85.19%	2.81	363.17	11.63%
medication with prescription		2.25		
medication without prescription		0.56		
Total costs per patient			**3,122.93**	**100.00%**

[1)] Costs are adjusted for base year 2007.

Healthcare-related costs

As Table 2.3 shows, patients with UPS consulted general practitioners, medical specialists and physiotherapists most. Almost all patients took medication, the most commonly being for pain without inflammation inhibition, for pain with inflammation inhibition, and for depression/anxiety. The mean of healthcare-related costs was estimated to be €3,122.93 (SD=€2,952.25) PPPY.

Table 2.4a. Distribution of total Dutch healthcare expenditures over main classifications [133]

Classification in this study	**Costs in million €**	**% of the total expenditures**
Unexplained Physical Symptoms: UPS	*3,312*	*4.4%*
Main classification	**Costs in million €**	**% of the total expenditures**
Blood and blood-forming organs	236	0.3%
Congenital malformation	250	0.3%
Perinatal diseases	419	0.6%
Skin and subcutaneous	802	1.1%
Inflammation diseases and parasitic diseases	1,064	1.4%
Pregnancy, childbirth and childbed	1,555	2.1%
Endocrine, dietary and metabolic diseases	1,707	2.3%
Urogenital system	1,907	2.6%
Accident, injuries and poisoning	2,141	2.9%
Respiratory system	2,618	3.5%
Blastomas (cancer and benign tumors)	3,423	4.6%
Nervous system and sense organs	3,981	5.3%
Symptoms and incompletely described syndromes	4,093	5.5%
Digestion system	4,879	6.6%
Musculoskeletal system and connective tissue	4,950	6.6%
Cardiovascular system	6,911	9.3%
Psychiatric disorders	15,895	21.4%
Not allocated/not illness related	17,615	23.7%
Total Dutch health care expenditure	**74,447**	**100.0%**

On the basis of this mean, the percentage of total Dutch annual healthcare expenditure associated with UPS was estimated to be over four percent (see Appendix A, which shows the calculation of this percentage). Comparison of this percentage with the percentages of all main disease categories [133] shows that the costs of patients with UPS were comparable to those in the category 'blastomas; cancer and benign tumors' (see Table 2.4a).

Comparison of the percentage of total Dutch annual healthcare expenditure associated with UPS with the percentages of patients with specific diseases and the

Table 2.4b. Healthcare expenditures in different reference populations [133]

Reference group	% of the total expenditures
General population	
general population aged between 15 and 65 years	48.9%
men aged between 15 and 65 years	23.3%
women aged between 15 and 65 years	25.6%
Psychiatric disorder (all disorders included)	
psychotic disorder (excluding schizophrenia)	0.1%
personality disorder	0.5%
anxiety disorder	0.6%
schizophrenia	1.2%
mood disorder	1.3%
alcohol and drugs dependence/misuse	1.4%
other psychiatric disorders	4.0%
(Unexplained Physical Symptoms: UPS	*4.4%)*
dementia	4.7%
mental retardation (including Down syndrome)	7.6%
Chronic physical condition (diseases with costs in the bottom and top five diseases included)	
–bottom five–	
congenital anomalies of nervous system	0.02%
meningitis	0.04%
hepatitis	0.04%
malignant neoplasm of ovary and other uterine adnexa	0.05%
chronic liver disease and cirrhosis	0.05%
–in between–	
Parkinson's disease	0.3%
multiple sclerosis	0.3%
cancer (colon, rectum, rectosigmoid junction, or anus)	0.4%
rheumatoid arthritis and other inflammatory polyarthropathies	0.7%
osteoarthritis and allied disorders	1.0%
disorders of soft tissues	1.1%
hypertension	1.2%
bronchitis, emphysema, asthma, bronchiectasis, extrinsic allergic alveolitis, chronic airway obstruction (including COPD)	1.3%
diabetes mellitus (including diabetic complications)	1.4%
–top five–	
rheumatic heart disease, diseases of endocardial structures, pulmonary circulation pericardium and endocardium, cardiomyopathy, conduction disorders, cardiac dysrhythmias	1.8%
diffuse diseases of musculoskeletal system and connective tissue	2.0%
cerebrovascular diseases (stroke)	2.2%
diseases of hard tissues of teeth	2.4%
chronic ischemic heart diseases	2.4%
(Unexplained Physical Symptoms: UPS	*4.4%)*

general population [133] shows that only patients with dementia and those with a mental retardation had higher costs (see Table 2.4b).

Work-related costs

Of the 162 patients with UPS, 73 (45%) had paid work, 34 of whom (46.6%) reported absence from work; 9 (12.3%) were partially absent, and 25 (34.3%) fully absent. In 15 of the 73 (21%) employed patients, this full absence had passed the end of the 23-week friction period. The mean number of lost working days per year due to absenteeism in employed patients was 67 (SD=94); after the exclusion of patients who had passed the end of the friction period, it was 43 (SD=74) disability days per year. The mean percentage of absenteeism in employed patients was 39.3% (SD=47.0); after exclusion of patients who had passed the end of the friction period, it was 23.5% (SD=39.5). The mean cost of productivity lost to absenteeism was estimated to be €5,334.72 (SD=€11,980.95) per employed patient per year, and €2,403.92 (SD=€8,442.89) PPPY (mean of the total study group).

Table 2.5a. Disability days per person per year and percentage of absenteeism in different reference populations

	N	Mean number disability days per year	Percentage of absenteeism
Study group			
Unexplained Physical Symptoms: UPS			
workforce	73	67.3	39.3
workforce within friction period	58	42.6	23.5
Reference group			
General population			
workforce [78]	23,000	7.5	4.2
working men [78]	12,489	7.4	3.7
working women [78]	10,511	7.7	4.7
Healthy workforce			
men and women [74]	14,697	not available	2.8
men [74]	7,980	not available	2.4
women [74]	6,717	not available	3.3
Workforce with chronic illnesses			
men and women [74]	8,303	not available	7.4
men [74]	4,509	not available	6.8
women [74]	3,794	not available	8.0
Workforce with specific chronic illness			
bipolar disorder [63]	30	55.5	not available
personality disorder [137]	743	27.7	not available

Both the mean number of disability days and the mean percentage of absenteeism of patients with UPS were compared with those of different reference populations [63; 74; 78; 137]. As Table 2.5a shows, patients with UPS had the highest number of disability days relative to those of other reference populations, even if patients who had passed the end of the friction period were excluded. Also, patients with UPS had the largest percentage of absenteeism compared with that of other reference populations.

Table 2.5b. Cost of presenteeism per person per year in different reference populations

	N	Mean annual cost per person with paid work due to presenteeism	
Study group		**€**	**US$**
Unexplained Physical Symptoms: UPS			
workforce	73	1,899	*2,520*
Reference workforce group			
General population			
healthy study controls [24]	61	572	*759*
Psychiatric disorder			
bipolar disorder [63]	30	*298*	395
personality disorder [137]	743	960	*1,274*
Chronic physical disease			
rheumatoid arthritis [24]	62	4,108	*5,450*

The exchange rate $/€ on 25 March 2012 was 1.3268.
Costs converted to another currency are written in *italics*.

Most working patients with no or only partial absence reported lower on-the-job productivity; only seven (14.6%) did not. The mean number of working hours lost per working patient due to this presenteeism was two hours per week (mean=2.0; SD=4.2) – over six percent (mean=6.3; SD=12.7) of their contracted hours. The mean cost of presenteeism was estimated to be €1,899.16 (SD=€5,248.08) per employed patient per year, and €855.79 (SD=€3,635.31) PPPY (mean of the total study group).

The mean cost of presenteeism of patients with UPS was compared with that of various reference populations [24; 63; 138]. As Table 2.5b shows, this mean was higher than that of patients with psychiatric disorders but lower than that of patients with rheumatic arthritis.

Disability and reduced efficiency were also reported in the performance of domestic tasks. Of the 162 patients with UPS, 89 (55%) asked other people to perform some domestic tasks for them for a duration of four hours (mean=4.3; SD=12.3) per week. For only 21 of these 89 patients (24%), domestic tasks were performed by paid professionals for a duration of almost three hours (mean=2.8; SD=1.9) per week. The mean cost of paid substitution of domestic tasks was estimated to be €433.27 (SD=€1,478.16) PPPY (mean of the total study group).

Total cost

The mean total cost, which included costs due to healthcare utilization and lost productivity in paid and unpaid work, was estimated to be €6,815.91 (SD=€10,923.14) PPPY.

Discussion

Main findings

We investigated QoL and healthcare-related and work-related costs in a general sample of patients with UPS, comparing them with those in other patient groups. Relative to other patient groups, patients with UPS reported the poorest QoL in the physical and social domains but not in the mental domain. Overall QoL summarized in utilities showed that the QoL of patients with UPS was still one of the poorest of all patient groups. Only patients with major depression had a lower utility.

Patients with UPS also had high healthcare-related and work-related costs: their mean healthcare-related costs were estimated to be €3,122.93 PPPY, representing an annual healthcare expenditure for UPS of more than three billion euros in the Netherlands alone – over four percent of the Netherlands' total annual healthcare expenditures. Relative to the total spectrum of diseases, only costs associated with dementia and mental retardation were higher. This was to be expected: these conditions require a high utilization of hospital and day hospital care services, which are the most expensive services in healthcare.

Work-related costs in patients with paid work were increased mainly by absenteeism. Absenteeism in patients with UPS was the highest of that in all patient groups: its mean cost was €2,403.92 PPPY. Societal costs were further increased by the mean cost of presenteeism (€855.79 PPPY) and of substitution of domestic tasks by paid professionals (€433.27 PPPY).

The mean total cost per patient with UPS per year was estimated to be €6,815.91.

Our principal findings in relation to the literature

Our findings on the different dimensions of QoL are comparable to those of earlier studies that compared patients with UPS and patients with major depression [38; 58; 79; 99]. Other studies also found that patients with UPS reported a poorer QoL in the physical domain and a relatively better QoL in the mental domain than patients with major depression. Unlike some studies which found that patients with UPS reported a poorer QoL in all domains than those with a medical diagnosis [135; 165], our findings indicated that this was the case only for the physical domain of QoL. In our study,

patients with UPS or a medical diagnosis were found to have a comparable QoL in the mental domain.

Our findings on the overall QoL summarized in utilities are in the range of those of earlier studies [58; 104; 118]. In these studies, the mean utility ranged from .47 to .70. This broad range may be caused by socio-economic characteristics which were most disadvantageous in the study with the lowest utility, and by comorbidity which was less severe in the study with the highest utility. The fact that our findings were in the middle of the range of utilities was to be expected as we had recruited a general sample of patients with UPS.

To relate our findings on the healthcare-related costs to the costs found in earlier studies, the mean healthcare-related costs of €3,122.93 PPPY found in our study were converted (at a euro-to-dollar exchange rate of €1=$1.3268) to $4,143.50. These costs are lower than the $5,678 PPPY estimated by Barsky et al. [14] and the $4,700 estimated by Smith et al. [135]. This difference might be due to differences in the healthcare systems and costs of healthcare services between the Netherlands and the United States. Our findings on the number of visits to healthcare services show both similarities and differences with earlier studies. While the eight medical specialist visits per year in our study are comparable with the seven visits found by Barsky et al. [14], the 15 primary care visits per year in our study are much higher than the four found by Barsky et al. [14]. Our findings are more comparable with studies of high-utilizing patients with UPS [136; 165], in which the mean number of visits per year ranged from 13.6 [136] to 15.9 [165]. This suggests that our study group belonged to the high-utilizing patients with UPS. This bias might have resulted from the fact that patients had to be referred by a physician, and that the chance of being referred increased with the number of visits. In contrast to the high number of primary care visits, the mean number of 0.24 hospital days PPPY in our study is extremely low. Smith et al. [135] found a mean of 1.9 hospital days per patient per three months. This difference might be related to the fact that our sample was drawn from a non-institutionalized population, which thus underrepresented hospitalizations.

Our findings on the work-related costs caused by absenteeism, which was based on the estimate of 67 disability days per employed patient per year, are comparable with the results of an earlier study [99], which found 18.2 disability days per three months in primary care patients with UPS. The study in question found that only patients with a depressive disorder had more disability days than patients with UPS, which were 22.5 disability days per three months.

Our findings on the work-related costs caused by presenteeism and paid substitution of domestic tasks, which were estimated to be €3,692.98 per patient with UPS per year, are considerably lower than those in chronic fatigue syndrome [124] and in common mental disorders [134]. For chronic fatigue syndrome, Reynolds et al. estimated the costs due to lost productivity at about $20,000 PPPY, 75% of which resulted from lost labor-

force productivity, with the remaining 25% due to lost household productivity [124]. Conversion of our monetary amounts to US dollars showed that the costs due to lost productivity amounted to only $4,900 PPPY, 88% of which resulted from lost labor-force productivity, with the remaining 12% due to paid substitution of domestic tasks. For depression, dysthymia, panic disorder, agoraphobia, social phobia, simple phobia, general anxiety disorder, alcohol abuse, and alcohol dependence, Smit et al. estimated the annual costs due to lost productivity per capita for the reference year 2003 in the Netherlands. These costs ranged from €10,302 for dysthymia to €375 for general anxiety disorder [134]. To compare our results with those in Smit's study, we converted the cost owed to lost productivity to annual cost per capita. This resulted in an annual per-capita cost of €367.56, which is much lower than that found by Smit et al. [134].

In our study, the work-related costs caused by loss of productivity in paid work might have been lowered due to the use of the friction-cost method, which led us to count only the cost of an absence from work of less than 23 weeks [62]. If we had counted absence from work irrespective of its duration (the so-called human-capital method), the number of patients with absenteeism would have doubled, thereby increasing the number of disability days even more. The work-related costs caused by loss of productivity in unpaid work might also have been lowered due to counting only the cost of lost household productivity that was substituted by paid professionals. If we had used total lost household productivity, the number of patients with lost household productivity would have been over fourfold.

Limitations of the study

A number of limitations merits attention. The data of our cross-sectional study were collected from a randomized controlled trial on the effectiveness of a cognitive-behavioral group training and not from an epidemiological study. As patients had to be referred to this trial by a healthcare provider and patients had to agree to take part in this treatment trial, our patient group might have been a selective group. Selection during the referral could have both increased and decreased QoL and costs; possible selection biases could have been only referring patients with more severe symptoms for reasons such as being those in great need or only referring patients with mild symptoms for reasons such as being best treatable in a relative short group training. Also, selection during the acquirement of patients' informed consent might have both increased and decreased QoL and costs; possible selection biases could have been only getting informed consent from patients with more severe symptoms for reasons such as being the most burdensome and eager to try or, alternatively, only getting informed consent from patients with mild symptoms for reason such as being the most vital to show up at their first appointment. When looking at the characteristics of our patient group and the results of our study, our patient group seems to be rather a general than a selective sample. The characteristics of

our sample can be described as mainly female, average age of 45 years, of whom 41% had a comorbid DSM-IV Axis I disorder and 29% had a comorbid DSM-IV Axis II disorder. These characteristics are in line with those found in other studies showing that UPS is more prevalent in women in their forties [38; 58; 79; 86; 135], and that 26 to 58% of the patients with UPS have a comorbid DSM-IV Axis I disorder and 37 to 88,6% have a comorbid personality disorder [37; 56; 57; 66; 76; 95; 100; 114; 127; 157]. Also, the results of our study appear comparable with those mentioned in earlier literature. Therefore, we believe that our patient group is a representative group for adult patients with UPS as defined in our study.

UPS in our study was defined as physical symptoms that fulfilled the DSM-IV criteria for an undifferentiated somatoform disorder or a chronic pain disorder. This definition is stricter than the general used definition of UPS which is physical symptoms that cannot be explained on the basis of known medical conditions. The prevalence of both undifferentiated somatoform disorder and chronic pain disorder in general practices totals 14.6% [38], while the prevalence of UPS in primary care is estimated to be at least 33% but can be as high as 74% depending on the definition and the methods used to classify UPS [85]. As costs in our study were calculated using a prevalence of only 14.6%, the real costs associated with UPS might be higher.

The QoL of patients with UPS was not adjusted for sociodemographic characteristics such as age, gender, education and living situation. Also, the QoL of the reference populations was not adjusted for sociodemographic characteristics. Not adjusting for sociodemographic characteristics might have affected our findings, as, in general, patients who are older or have a low education report a poorer QoL in the physical domain, and patients who are female or not living with a partner report poorer QoL in the mental domain [145]. Interestingly, patients with UPS, who are mainly female, reported a relatively better QoL in the mental domain than in the physical domain. Adjusting for the effects of sociodemographic characteristics seems to be artificial, as some illnesses, such as UPS and breast cancer, have different prevalence's in various sociodemographic groups. By eliminating the effects of sociodemographic characteristics, results will visualize the burden of the illness itself and not the total burden of patients, whereas treatments are indicated on the latter condition.

QoL and costs were not adjusted for comorbid mental and somatic disorders. As comorbidity reduces QoL [38; 145] and increases costs [14], the QoL reported might have been lower and costs might have been higher due to the comorbidity prevalent in our study. However, isolating these effects would also reduce generalizability, as patients with UPS suffer from many comorbid mental and somatic disorders. The number of comorbid anxiety or depression disorders in patients with UPS is higher than that in either healthy controls or in patients with phenomenologically similar medical diseases of known organic pathology [67]. The number of comorbid personality disorders in patients

with UPS is higher than that in patients with a mood and/or anxiety disorder [56]. The number of comorbid somatic disorders in UPS is higher than that in general primary-care patients [14; 165]. These numbers suggest that this comorbidity is an essential part of UPS.

Another potential limitation is that QoL and costs were measured using self-report questionnaires. Potentially, self-report is subject to errors caused by recall difficulties. Recall is easier: 1) if the time-period between the event and the recall is shorter, a two-week interval having been suggested as best; and 2) if events fluctuate dramatically [50]. As the recall period of the questionnaire used on QoL and on the healthcare-related costs was four weeks, and as work-related events are likely to have fluctuated only slightly or moderately, errors in the recall may have followed.

The self-report data on costs were extrapolated to estimate costs at a one-year interval, an approach that would be appropriate only if the short intervals were chosen at random and were thereby generalizable. If this assumption was not met, the sample would have produced an inaccurate estimate. As our findings on the number of visits to healthcare services and the number of disability days are reasonably comparable with those of earlier studies in patients with UPS [14; 99; 136; 165], we believe that the short intervals are also reasonably generalizable.

Work-related costs were based on a small sample of patients that resulted partly from our use of the friction-cost method and might have been caused partly by the long duration of UPS in our study group. As our patients had had their symptoms for a long time, their risk of having lost paid employment and thereby not participating in the workforce anymore was high.

Our study also has several strengths. We examined QoL and costs in patients with UPS who were referred both by primary and secondary services. The resulting heterogeneous population makes our results more generalizable than those of most studies that explored only the burden of UPS in primary care [14; 38; 58; 79; 99; 135; 165]. QoL was measured using a generic instrument, from which utilities could be derived. The use of such instrument enabled us to compare the domains and overall QoL with those in several reference populations. Costs were measured using a generic instrument that measured not only healthcare-related costs, but also work-related ones. Similarly, by comparing the costs regarding patients with UPS with those regarding various reference populations, we gained insight into the relative magnitude of these costs. Finally, our study investigated not only healthcare-related and work-related costs per se, but also examined a broad spectrum of related outcomes, including the number of healthcare visits, the percentage of total annual healthcare expenditures, the number of disability days, the percentage of absenteeism, the number of working hours lost to presenteeism, the percentage of presenteeism, and the hours of substitution for domestic tasks. These outcomes, in contrast to costs solely, can all be compared internationally, i.e.

across countries which have different health care systems, healthcare services and labor markets.

Clinical and policy implications

Information on QoL of specific patient groups and on the costs associated with them, and on how these relate to corresponding data in other patient groups is helpful in allocating healthcare resources. Our finding with regard to patients with UPS – that their QoL was one of the poorest of all patient groups – is a clear reminder that they are in great need and that the allocation of sufficient resources is justified. Interestingly, as their healthcare-related costs were among the highest, they already use a high level of resources. This seems to suggest that the solution does not lie in increasing healthcare expenditure on patients with UPS. Instead, our findings raise the question of whether these resources are used properly.

Currently, physicians are the resource used most by patients with UPS – a use that is consistent with patients' perspective on their symptoms [30]. Relative to patients with a medical diagnosis, those with UPS attribute their physical symptoms more to physical causes [112], less to lifestyle factors [112] and comparably to emotional causes [83; 112]. Although physicians are essential to the diagnosis of UPS – a thorough medical examination being necessary to the exclusion of known medical diseases – their role in its treatment is less obvious. The most effective treatment for UPS is cognitive-behavioral therapy conducted at specialized centers or by mental health professionals [4; 86; 122; 152]; cognitive-behavioral therapy conducted by general practitioners showed no conclusive effect [3; 9; 12; 105; 126; 153; 156]. This is to be expected, as specialized centers and mental health centers conduct a much higher volume of cognitive-behavioral therapy, which is known to be related with better outcome [64]. However, specialized centers and mental health centers are not easily accessible to patients [36], their treatment capacity is limited, and, perhaps most important of all, patients refuse to be referred to the mental health centers because of their physical perspective on UPS [5; 122].

Overall, our findings suggest that better outcome might be achieved if medical and mental healthcare services collaborated more closely resulting in cognitive-behavioral therapies conducted by mental-health professionals located at medical healthcare institutions and hospitals. This therapy should be available for a potentially large group of patients, be easily accessible, and tailored to patients' perspectives. To the extent that such cognitive-behavioral therapy is cost-effective, the QoL of patients will be improved and healthcare-related and work-related costs will be reduced.

Conclusions

Patients with UPS have a high burden of disease and use considerable amount of healthcare resources. This burden for both patients and society helps to justify the allocation of sufficient resources to effective treatment for these patients.

Acknowledgements

The authors would like to thank Jordi J.F. Butterhoff, pharmacist and head of the hospital outpatient pharmacy at the Academic Medical Center in Amsterdam, the Netherlands, for his advice on classifying medication and on calculating the prices of pharmacological interventions.

The authors would like to thank Hanneke C.J.M. de Haes, head of the department of Medical Psychology at the Academic Medical Center in Amsterdam, the Netherlands, for her constructive comments.

Chapter 3

The effectiveness of a training for patients with unexplained physical symptoms: protocol of a cognitive-behavioral group training and a randomized controlled trial

Abstract

Background

In primary care, the prevalence of Unexplained Physical Symptoms (UPS) can reach as high as 74%. UPS can cause high levels of distress and healthcare utilization. Cognitive-behavioral therapy has shown to be effective, but does not seem to be attractive to patients. An exception is a therapy based on the consequences model, which distinguishes itself by its labeling of psychosocial distress in terms of consequences rather than as causes of UPS. In secondary care, 81% of the patients accepts this therapy, but in primary care the outcome is poor. We assume that positive outcome can also be reached in primary care, if the consequences model is modified and used bottom-up in an easily accessible group training, in which patients are relieved of being blamed for their symptoms. Our aim is to investigate the effectiveness and cost-effectiveness of this training.

Methods/design

A randomized controlled trial is designed. One hundred patients are randomized either to the group training or to the waiting list.

Physicians in general practices and outpatients clinics of general hospitals refer patients. Referral leads to inclusion if patients are between 18 and 65 years old, understand Dutch, have no handicaps impeding participation and the principal DSM-IV-TR classification is undifferentiated somatoform disorder or chronic pain disorder. In contrast to other treatment effect studies, the co-morbidity of a personality disorder does not lead to exclusion. By this, we optimize the comparability between the study population and patients in daily practice enlarging the generalization possibilities.

We choose quality of life (SF-36) instead of physical symptoms as the primary outcome measure. The SF-6D is used to estimate Quality Adjusted Life Years (QALYs). The TiC-P is used to measure costs. Measurements are scheduled at baseline, after the training or waiting list, three months after the end of the training, and twelve months after the end of the training. The differences between measurements are analyzed according to the intention-to-treat principle. The cost-effectiveness is expressed as costs per QALY, using multiple sensitivity analyses on the basis of a probabilistic model of the trial.

Discussion

If we show that our group training is effective and cost-effective, more patients could be served, and their quality of life could be improved while costs might be reduced. As the training is investigated in a heterogeneous patient group in the daily practice of a mental healthcare institution, its transfer to practice should be relatively easy.

Background

The estimated prevalence of unexplained physical symptoms in primary care ranges from 18 to 74% [12; 85]. This huge difference in estimating prevalence is caused by multiple definitions of unexplained physical symptoms such as Unexplained Physical Symptoms (UPS), Medical Unexplained Physical Symptoms (MUPS), functional somatic syndromes and abridged somatization. We use the Diagnostic and Statistical Manual of Mental Disorders IV –Text Revision (DSM-IV-TR) [7] and define unexplained physical symptoms with the classification of 'undifferentiated somatoform disorder' and 'chronic pain disorder'. In general practices, the prevalence of undifferentiated somatoform disorder is 13.0% and the prevalence of chronic pain disorder is 1.6% [38]. In general, the DSM-IV-TR classifies symptoms without making assumptions about etiology. However, the DSM-IV-TR does presume psychological causes in the beginning, severity, increase or continuation of pain in chronic pain disorder. Therefore, we prefer to use the mere descriptive term 'Unexplained Physical Symptoms' (UPS).

Patients with UPS have high levels of psychosocial distress and healthcare utilization [15], for which cognitive-behavioral therapy has shown to be most effective [86; 98; 111; 152]. However, it is widely believed, that patients with UPS reject this kind of therapy. The consequences model is a positive exception. The key difference of this model compared with other cognitive-behavioral models is its labeling of psychosocial distress in terms of consequences rather than as causes of UPS. Herewith, the consequences model fits both professionals' and patients' point of view. Refraining from labeling psychosocial distress as causes of UPS corresponds with the lack of consensus among professionals about the causes of UPS, which is reflected in the ongoing debate about the position of somatoform disorders on Axis I or III in the next edition of Diagnostic and Statistical Manual of Mental Disorders [54; 87]. Moreover, labeling psychosocial distress as consequences matches the patients' perspective of UPS. This is reflected in the fact, that 81% of the patients in an academic medical care service accepts an individual therapy based on the consequences model [142] and this individual therapy has positive outcomes in secondary care [144]. Unfortunately, in primary care, this high acceptance rate could not be reproduced and therapy based on the consequences model resulted in poor outcome [10; 12].

We assume that the consequences model can maintain its positive outcome for patients in primary care, if we make some modifications. Firstly, we tailor this model more accurately to patients' perspective of their physical symptoms. Moreover, we put additional attention to relieve patients from being blamed for their symptoms. Furthermore, we make the group training easy accessible. Our aim is to investigate the effectiveness and cost-effectiveness of this easily accessible group training for patients in primary care conducted in the daily practice of our mental healthcare institution, Riagg

Rijnmond, the Netherlands. This study protocol provides a detailed description of the cognitive-behavioral group training and the design of the randomized controlled trial investigating the effectiveness and cost-effectiveness of this training.

Objectives

The primary aim of this study is to investigate the effectiveness and cost-effectiveness of our easily accessible protocolized group training for patients with UPS in primary care conducted in the daily practice of a mental healthcare institution. The secondary aim is to identify variables which enable us to predict the effectiveness.

Methods/design

Design

The effectiveness and cost-effectiveness of the group training are evaluated in a randomized controlled trial (see Figure 3.1).

The study started February 2005. The inclusion of patients has ended in September 2008. The one-year follow-up period of the randomized patients will be finished in April 2010.

Study population

Patients are included when:

1. they are between 18 and 65 years old;
2. they are able to speak, read and write Dutch;
3. their UPS persists at least 6 months;
4. their UPS is classified as undifferentiated somatoform disorder or chronic pain disorder according to the criteria of the *Structured Clinical Interview for DSM-IV Axis I Disorders/Patient edition* (SCID-I/P) [55].

Patients are excluded when:

1. UPS is not the principal somatic disease;
2. undifferentiated somatoform disorder or chronic pain disorder is not the principal DSM-IV-TR classification;
3. handicaps, like cognitive mental impairment and/or blindness, impending the patient to participate in the training.

To optimize the comparability between the study population and the patients with UPS in daily practice and to make generalization to daily practice possible, we have decided that having a personality disorder is not an exclusion criterion; this is in contrast to other treatment effect studies. We do measure personality disorder using the *Vragenlijst Kenmerken van Persoonlijkheid* (VKP) - a self-report questionnaire for

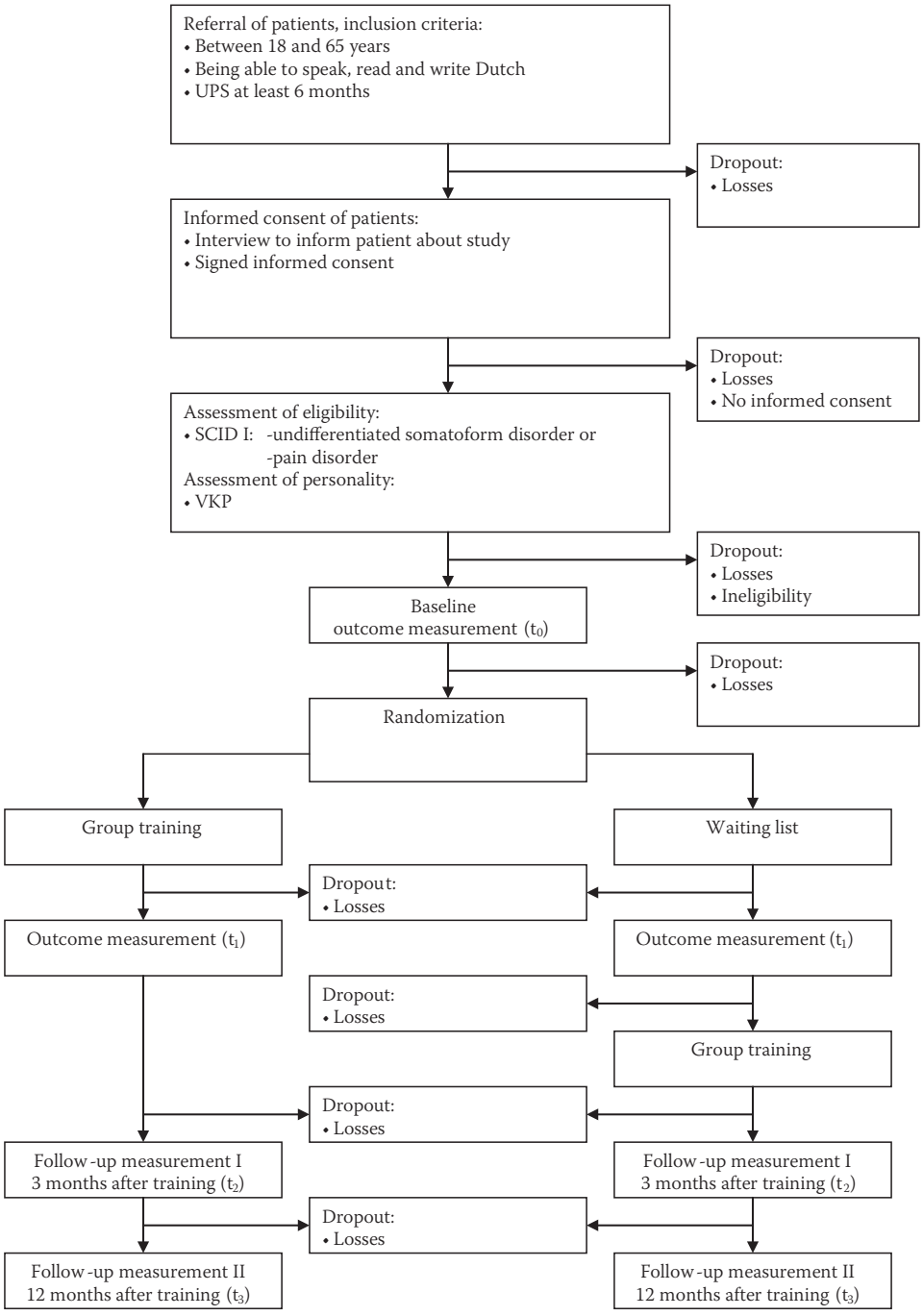


Figure 3.1. Flow diagram of the randomized controlled trial

DSM-IV Axis II personality disorders based on the International Personality Disorder Examination (IPDE) [46]. By measuring personality disorders using this instrument, we can describe the study population not only in terms of personality disorders, but we can also identify the influence of personality disorders on effectiveness.

Patients are recruited from general practices and outpatient clinics of general hospitals in and nearby Rotterdam, the Netherlands. Physicians' attention is drawn to the group training by periodical postcards informing them when and how they can refer patients to the group training. Patients' attention is drawn to the group training by announcements in local newspapers and on websites of patients' associations, in which they are asked to make an appointment with their physician to discuss referral when interested. Physicians decide whether the physical symptoms are medically explained or unexplained hereby checking the first *exclusion* criterion, after which they refer patients if they find this appropriate. After referral, patients are invited for an interview, preferably in a medical setting, in which they are verbally and in writing informed about the study. In this interview, the first three *inclusion* criteria and the last *exclusion* criterion are verified. After receiving patients' signed informed consent, patients are invited for a second interview, in which the last *inclusion* criterion and the second *exclusion* criterion are investigated by the Structured Clinical Interview for DSM-IV Axis I Disorders/Patient edition (SCID-I/P), administered by independent psychologists. These psychologists make the final decision based on the results of the SCID-I/P whether patients' UPS can be classified as an undifferentiated somatoform disorder or as a chronic pain disorder and whether this disorder is the principal DSM-IV-TR classification. If undifferentiated somatoform disorder or chronic pain disorder is the principal DSM-IV-TR classification, then patients complete the self-report questionnaire for DSM-IV Axis II personality disorders (VKP).

Right before the start of each training, the newly included patients complete the outcome questionnaires. Subsequently, an independent statistician randomizes them either to the group training or to the waiting list with a computer-based 1:1 ratio randomization procedure. The results of this randomization procedure are sent to the patient by letter. If randomization leads to starting with the group training, then an invitation for the group training is enclosed in the randomization letter. After the group training or after a waiting-period of the same length as the group training, all patients complete the outcome questionnaires for the second time.

After completing in the outcome measurements for the second time, the patients on the waiting list are invited to the group training. They attend the group training after their waiting period together with the newly included patients randomized to the group training. For patients on the waiting list, a longer waiting period is not feasible, because the study is conducted in the daily practice of a real life mental healthcare institution. By combining the patients assigned by the randomization to the waiting list with the patients

assigned by the next randomization to the group training in the same training, patients in both conditions receive exactly the same training. After attending the training, all patients complete follow-up measurements at three months after the end of the training and once more at one year after the end of the training.

Experimental condition: group training

The group training [170] is based on the consequences model, which labels psychosocial stress as consequences rather than as causes of UPS to prevent the suggestion that 'it is all in their mind'. The original consequences model [140] assumes that UPS induces irrational beliefs regarding the symptoms resulting in consequences, which maintain or increase UPS (see solid arrows in Figure 3.2). Its implementation in an individual therapy starts with beliefs, which are labeled as irrational, disputed and replaced with rational ones. Subsequently, other consequences are changed to break the vicious circle [141]. The ultimate goal is to reduce physical symptoms.

We feel that this original consequences model has not completely succeeded in preventing the 'it is all in the mind' suggestion. After all, patients might perceive the focus on irrational beliefs still as 'it is all in the mind'. Patients might experience the disputing of these beliefs as blaming or belittling. Blaming and belittling result in a rejection of the

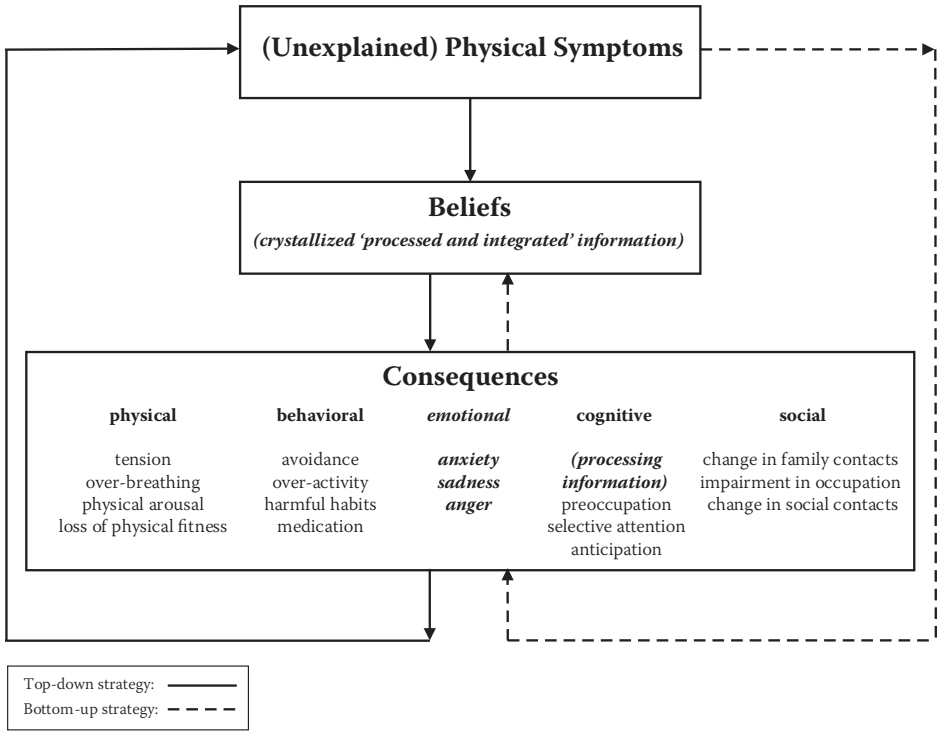


Figure 3.2. The *tailored* consequences model

therapy by patients and in poor outcome [91; 169]. That is why we tailor the consequences model for our group training (see dotted arrows in Figure 3.2). Our group training focuses on the visible consequences, labeling them as survival strategies in reaction to physical symptoms, justifying their existence by their benefit in short term albeit indicating their harmfulness in the long run, and therefore replacing them with long run beneficial strategies. Subsequently, the underlying beliefs of these survival strategies are explored, checked and, if necessary, changed in more helpful ones. Finally, the problem-solving model of Nezu et al. [110] is introduced to facilitate developing personal effective survival strategies for all kinds of problems, acknowledging that physical symptoms can increase the number of problems. The ultimate goal is not reducing physical symptoms as with the original consequences model, but is improving quality of life.

In summary, the group training approaches the consequences model bottom-up instead of the commonly used top-down approach. By approaching the consequences model bottom-up (starting with consequences and unconditionally accepting and justifying their existence) instead of top-down (starting with addressing irrational beliefs and disputing them), we reach a closer match with the patients' physical point of view. Moreover, patients are relieved from being blamed, called exoneration, by justifying the existence of consequences by their benefit in short term, by which we facilitate compliance. Furthermore, we tailor the setting of the training to patients' physical point of view by organizing the training in a medical healthcare setting and not in our own mental healthcare institution. This also avoids the implicit but unintended 'it is all in the mind' suggestion.

This bottom-up approach results in a group training comprising thirteen ad verbatim protocolized weekly sessions of two hours each.
After session 1, the structure of each session is as follows:

- sharing experiences of the past week;
- discussing home-assignments;
- doing a group breathing and relaxation exercise;
- identifying short-term beneficial survival strategies and modifying them into long-term beneficial ones;
- ending with a summary of the session and new home-assignments.

Each session is built around a theme. In session 1, trainees get acquainted with each other by telling each other about their symptoms and by setting their personal goals for the training.

In session 2, the flight-fight cycle and habits in reaction to symptoms are identified as survival strategies of the body. The flight-fight cycle is modified with the learning of the breathing and relaxation exercise and the habits are reshaped into long-term beneficial ones.

In session 3, avoidance and overactivity in reaction to symptoms are identified as survival strategies of the body. These reactions are modified by scheduling different kinds of activities in a feasible pace alternated with short breaks (5 to 10 minutes) that is compatible with the trainees' physical condition.

In session 4, emotions in reaction to symptoms are identified as useful survival strategies indicating the need for problem-solving. Moreover, the physical symptoms of emotions are pinpointed and reduced or even relieved with the breathing and relaxation exercise.

In session 5, thoughts in reaction to symptoms are identified as survival strategies of the mind and, if necessary, they are modified with the Ellis' ABC scheme into more helpful ones.

In session 6, a good physical shape is identified as an effective survival strategy of the body, which can be achieved by doing a low cardiac physical activity (like walking or biking) twice a day and by increasing this up to a maximum of 60 minutes twice a day, after which physical shape can be maintained by a regular sport twice a week.

In session 7, the diagram in Figure 3.2 is filled in by the trainees and discussed afterwards with an important and trusted person in his or her own social environment.

In sessions 8 to 12, the five steps of the problem-solving method (1. problem-attitude, 2. problem-definition, 3. alternative solutions, 4. solution plan, and 5. solution implementation and evaluation) are identified and practiced.

In session 13, a personal First Aid Kit is composed out of the learned long-term beneficial survival strategies aimed to prevent relapse.

Control condition: waiting list

Patients assigned to the waiting list condition wait during the group training of 13 weeks, after which they start with their training.

Outcome measurements

Effectiveness and cost-effectiveness are measured using three self-report questionnaires, which are sent to patients' home to be completed before randomization, at the end of the training or waiting list period, at 3 months after the end of the training and once again at 12 months after the end of the training (see Figure 3.1).

1. The *36-item Medical Outcomes Study Short-Form General Health Survey* (SF-36) [168]

   The SF-36 measures functional health and well-being during the past four weeks with the following eight multi-item scales: Physical functioning, Role functioning physical, Bodily pain, General health, Vitality, Social functioning, Role functioning emotional and Mental health. The scores of the SF-36 can also be summarized in the 'Physical component summary' and the 'Mental component summary' [167]. Furthermore, a

utility score can be derived from 11 items of the SF-36. These 11 items define six dimensions of health, the SF-6D; Physical functioning, Role limitations (Role functioning physical in combination with Role functioning emotional), Bodily pain, Social functioning, Vitality and Mental health. The outcome of the SF-6D can be converted into Quality Adjusted Life Years (QALYs), the preferred outcome in health economics, using formerly called 'valuations studies' [25].

2. The *revised 90-item Symptom Checklist* (SCL-90-R) [13]
   The SCL-90-R measures a broad range of symptoms and their intensity during the past week with the following eight multi-item scales: Phobic anxiety, Anxiety, Depression, Somatization, Obsessive-compulsive, Interpersonal sensitivity, Hostility and Sleep difficulties. The scores of the SCL-90-R can be summarized in the 'Global severity index', reflecting the overall psychological distress.
3. The *Trimbos/iMTA Questionnaire for Costs associated with Psychiatric Illness* (TiC-P) [62]
   The TiC-P measures direct medical costs due to healthcare utilization during the past four weeks, excluding the group training itself. The costs of the training itself are calculated using the records of the institution. The TiC-P also registers the indirect non-medical costs due to productivity loss during the past two weeks. This second part of the questionnaire about indirect costs is based on the short form of the Health and Labour Questionnaire (HLQ).

Outcome measurements: clinical evaluation

The aim of the clinical evaluation is to investigate the effectiveness of the group training by comparing the improvement of quality of life gained in the training group with the improvement in the waiting list group. Primary outcome measure is 'Physical component summary' and the 'Mental component summary' of the SF-36. Secondary outcomes are the eight individual scales of the SF-36 and the scales of the SCL-90-R.

Outcome measurements: economic evaluation

The aim of the economic evaluation is to investigate the cost-effectiveness of the group training in terms of cost per Quality Adjusted Life Years (QALYs). QALYs are estimated by converting SF-6D into utilities by means of the preference-based UK tariff [25]. Indirect costs for employed patients are measured using the TiC-P by the reported duration of sick leave and the production loss without sick leave. The indirect costs of production loss due to sick leave are computed by multiplying the number of sick leave's day with the average net income per worker related to age and gender. For a long-term sick leave, the friction-cost method is applied to assess the productivity loss, using a friction period of five months.

Sample size calculation

To determine the required sample size for measuring differences in quality of life between the two conditions (group training and waiting list), the sample size is calculated by power analysis. The effect size of cognitive-behavioral therapy for quality of life is not well known, because, in other effect studies, the outcome is usually measured in terms of physical symptoms. Therefore, we have to use effect size of cognitive-behavioral therapy for physical symptoms as an available estimator for the (shortage of) quality of life. The effect size of cognitive-behavioral therapy for physical symptoms ranges from 0.00 to 0.95 [111], suggesting a medium effect for cognitive-behavioral therapy for physical symptoms. Assuming this effect also applies for quality of life, the magnitude of the effect size following Cohen's (1988) [34] is 0.50. With a power of 0.80 and an alpha of 0.05 (two-tailed), a sample size of 100 patients (50 in each condition) is required.

Statistical analyses

The comparability of the patients' baseline-variables between the two conditions (group training and waiting list) is analyzed with the two-tailed t-tests for independent samples for the continuous variables, with the two-tailed Mann-Whitney U-tests for the ordinal variables and with the chi-square tests for the categorical variables. If the patients in the two conditions are not comparable on one or more baseline-variables, those variables will be utilized as covariables in the subsequent analyses.

Statistical analyses: clinical evaluation

The clinical evaluation is conducted according to the intention-to-treat principle. The effectiveness of the group training for the primary and secondary outcome measures is analyzed with mixed modeling (i.c. random regression modeling). Baseline measurements, corresponding to the subsequent outcome measurements, are entered as covariables. This method of mixed modeling for repeated measurements enables the use of flexible error covariance structures. In addition, the predictive performance of baseline-variables, especially personality variables, on effectiveness can be estimated.

Statistical analyses: economic evaluation

The economic evaluation is conducted from a societal perspective, the preferred perspective in health economic evaluations [44]. This means that all costs are included: the direct medical costs, the indirect medical costs and the indirect costs associated with productivity loss of patients. Adopting a societal perspective also means that all relevant effects and all costs beyond the time frame of the trial should be measured. In this case, the differences between the group training and the waiting list can only be measured empirically till 13 weeks, but relevant effects and costs might occur beyond

that artificial time horizon. For this reason, we will estimate effects and costs till two years, using a Markov model [28]. By making the Markov model probabilistic, we will be able to implement multiple sensitivity tests simultaneously and test for specific model assumptions. A critical assumption will be the extrapolation of the effect beyond 13 weeks. This assumption will be explored by calculating the minimal duration that the group training should be effective, in order to achieve a satisfactory level of cost-effectiveness.

Ethical considerations

The Medical Ethical Committee of Erasmus Medical Center, Rotterdam, The Netherlands, has approved this study, registered under MEC-2004-191. The study is also registered in the Dutch Trial Register (NTR 1609) [171].

Discussion

The primary aim of our study is to investigate the effectiveness and cost-effectiveness of an easily accessible protocolized group training for patients with UPS in primary care in the daily practice of our mental healthcare institution, Riagg Rijnmond, the Netherlands.

Investigating the effectiveness and cost-effectiveness of our training in the daily practice of a mental healthcare institution has its benefits and its limitations. The huge advantage of investigating in the daily practice is that if effectiveness and cost-effectiveness are shown, the group training can be started without the delay of practical implementation issues. The limitations for this study are fewer possibilities for exclusion of patients and for the control condition.

Consequently, the effectiveness and cost-effectiveness are explored in a heterogeneous group of patients. Measuring the heterogeneity of our study population using the SCID-I/P and VKP but not excluding patients with psychiatric co-morbidity, and drawing attention to the group training by announcements to both physicians and patients increase heterogeneity. Patients being referred on their own initiative are probably more motivated than patients being referred on their physician's initiative. On the one hand, this enhances the probability of a representative study population, whose heterogeneity will be equally divided between the two conditions by randomization. Furthermore, this heterogeneous study population is real practice, making the study's results a realistic estimate of that practice. On the other hand, the group training might be effective by only treating the co-morbidity, like anxiety. Analyzing the predictability of this co-morbidity and other baseline variables on the effectiveness and cost-effectiveness can solve this limitation.

Because the daily practice only allows a waiting list for a short period, the follow-up measurements do not have a control condition. Repeated measurements in the same patients and using a probabilistic model can solve this problem partially.

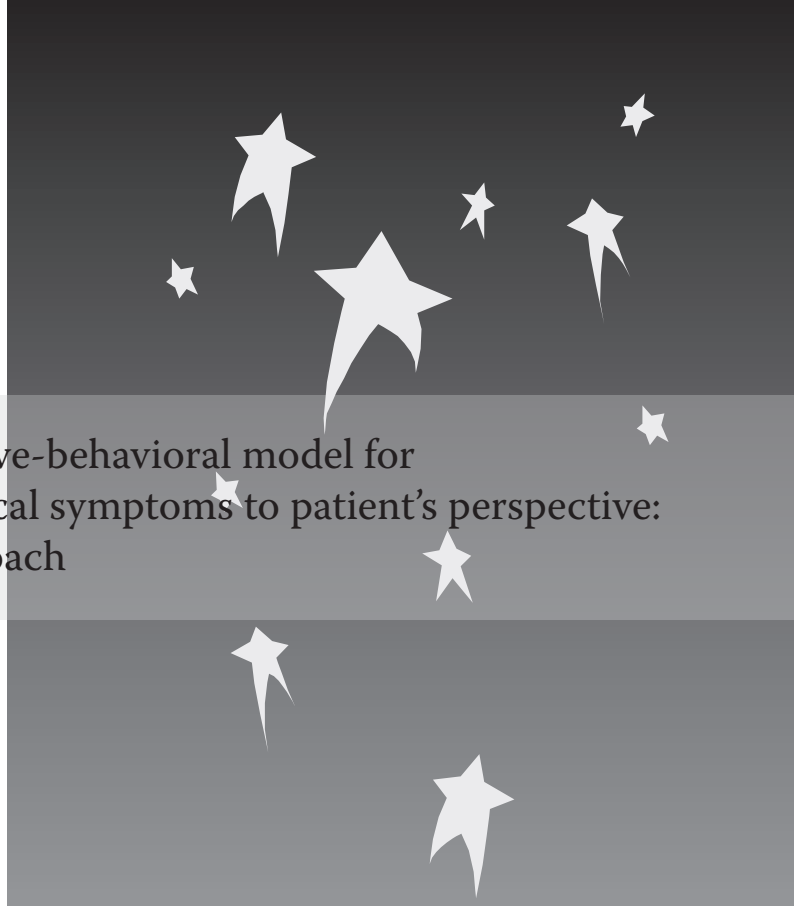
If we show that our group training is feasible in daily practice, effective, and cost-effective, more patients with UPS could be served, and their quality of life could be improved while costs might be decreased.

Acknowledgements

The first author is indebted to Riagg Rijnmond, the Netherlands. This study could not have been designed without the colleagues, financial support and facilities of Riagg Rijnmond.

Her considerable appreciation and gratefulness go to the late H. Methorst, psychiatrist and psychoanalyst at Riagg Rijnmond, whose trust in and support to the author she will always remember. The authors' considerable appreciation and gratefulness also go to the late professor R.W. Trijsburg PhD, who supervised the development and start of the study.

Chapter 4



Tailoring a cognitive-behavioral model for unexplained physical symptoms to patient's perspective: a bottom-up approach

Abstract

The prevalence of Unexplained Physical Symptoms (UPS) in primary care is at least 33%. Cognitive-behavioral therapy has shown to be effective. Within cognitive-behavioral therapy, three models can be distinguished: the reattribution model, the coping model and the consequences model. Therapy based on the consequences model, which labels psychosocial stress in terms of consequences rather than as causes of UPS, has high acceptance among patients and is effective in academic medical care. This acceptance and effectiveness are lost when applied in primary care. To increase acceptance of therapy based on the consequences model among patients in primary care, we tailor this model to patient's perspective by approaching the model bottom-up instead of top-down. Subsequently, we use this tailored model in an easily accessible group training. We describe our approach using two illustrative cases.

Introduction

In primary care, the prevalence of Unexplained Physical Symptoms (UPS) is estimated to be about 33% [85]. For UPS, cognitive-behavioral therapy has shown to be most effective in secondary care, while evidence for its effectiveness in primary care is less distinct [86; 122; 152]. Within cognitive-behavioral therapy for UPS, three models can be distinguished: the reattribution model, the coping model and the consequences model [160]. In the reattribution model, the line of reasoning is that the cause of UPS is psychosocial stress, depression or anxiety. The reattribution model aims to explain how symptoms can relate to psychosocial problems, depression or anxiety (reattribution) to alleviate UPS or to treat any underlying psychological or social problems. In the coping model and the consequences model, the line of reasoning is that the cause of UPS is unknown. The coping model aims to cope with the UPS to reduce stress, whereas the consequences model aims to change the consequences of UPS that maintain UPS to alleviate UPS.

The consequences model is most interesting because it combines the benefits of the other two models. It shows the interaction between body and mind, and it also labels psychosocial stress as consequences rather than as causes, preventing the suggestion that 'it is all in the mind'. Moreover, 81% of the patients in an academic medical setting accepts a therapy based on the consequences model [142]. A therapy based on this model (Figure 4.1: solid arrows) starts with disputing the beliefs in reaction to UPS as irrational and replacing them with rational ones, followed by changing the consequences to break the vicious circle [140; 141]. In an academic medical setting, this therapy is shown to be effective [144]. However, in primary care, the acceptance of a group therapy based on the consequences model drops, despite of the use of the same procedure and methodology introduced to patients by the same person. This low acceptance makes this approach of the consequences model not feasible for primary care [12], while the high prevalence of UPS and patients' burden caused by UPS ask for a high acceptable and easily accessible cognitive-behavioral treatment of UPS.

We wish to tailor the consequences model more closely to patients' perspective in that it can lay the foundation of a highly acceptable and easily accessible cognitive-behavioral group training for patients with UPS in primary care. We assume that patients in primary care have a physical perspective of their symptoms in that they formulate their complaints in terms of physical problems. Therefore, we approach the consequences model bottom-up (Figure 4.1: dotted arrows) starting with UPS and visible physical consequences instead of top-down (Figure 4.1: solid arrows) starting with UPS and the psychological beliefs. In this bottom-up approach, the visible consequences are labeled as survival strategies, of which existence is beneficial and justified in short term but harmful in the long run. Therefore, these strategies should be replaced by beneficial

strategies in the long run. Subsequently, the underlying beliefs of these strategies are explored and, if necessary, adapted to reality to make them also beneficial in the long run. The newly acquired information about the differences in survival strategies and their own growing experiences with new strategies will make this adaptation easier. Finally, the problem-solving model of Nezu et al. [110] is introduced to facilitate the development of personal effective survival strategies for all kind of problems, acknowledging that physical symptoms may increase the number of problems. The ultimate aim is to improve quality of life.

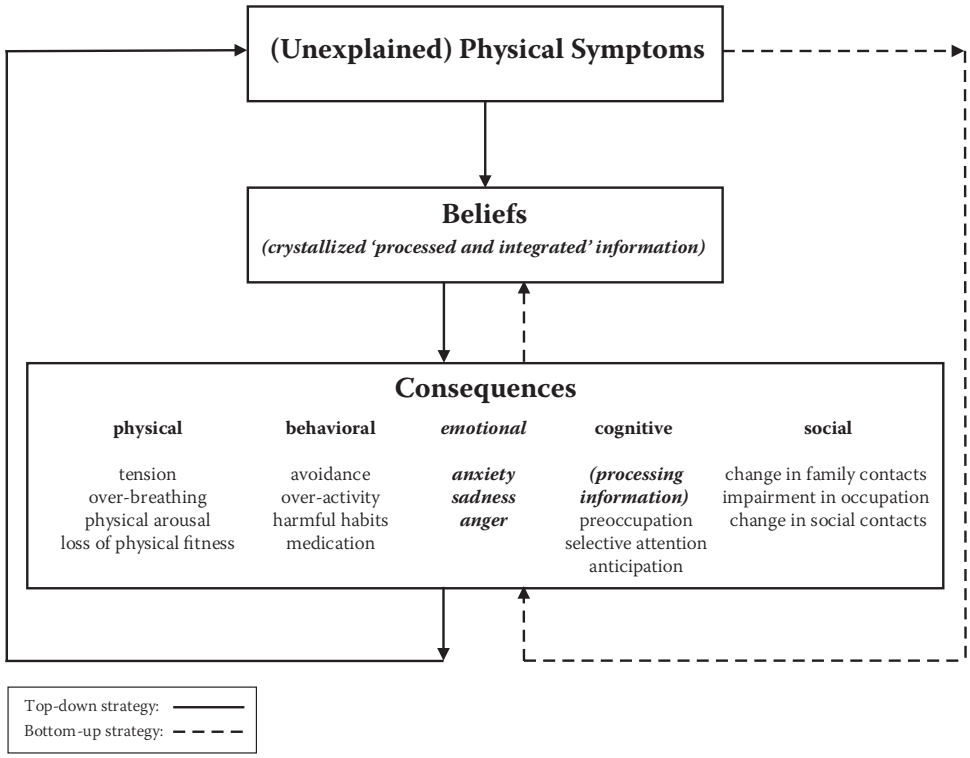


Figure 4.1. The *tailored* consequences model

The bottom-up approach results in 13 weekly protocolized training sessions of two hours each. After session 1, each session has the following structure:

- sharing experiences of the past week;
- discussing home-assignments;
- doing a group breathing and relaxation exercise;
- identifying short-term beneficial survival strategies and modifying them into long-term beneficial ones;
- ending with a summary of the session and new home-assignments [170; 173].

Table 4.1. The long-term beneficial survival strategies introduced in each session

Session(s)	Long-term beneficial survival strategies
1	Getting acquainted with each other Setting personal goals for the training
2	Practicing the breathing and relaxation exercise Substituting the habits with potential harmful effects in the long run with incompatible beneficial habits
3	Scheduling different kind of activities in a feasible pace with short breaks preventing avoidance and overactivity
4-5	Identifying emotions and thoughts, and optimizing them with the Ellis' ABC scheme
6	Improving one's physical shape by doing a daily low cardiac physical activity Expanding this physical activity with one minute every day
7	Discussing consequences of physical symptoms with an important and trusted person
8-12	Practicing the five steps of the problem-solving method (1. problem-attitude, 2. problem-definition, 3. alternative solutions, 4. solution plan, and 5. solution implementation & evaluation)
13	Assembling the long-term beneficial survival strategies in a personal First Aid Kit to prevent relapse

Table 4.1 shows the long-term beneficial survival strategies introduced in each session.

The training may be made easily accessible by implementing it on a location preferred by primary care physicians and patients. Furthermore, easy access to the training may be also reached by asking primary care physicians only to confirm UPS and to refer to the training. This role may be welcome to most of the primary care physicians, because they view medical investigation as their core business and evaluate their psychological skills for patients with UPS as insufficient [128]. Referral to the training may be acceptable for patients because of its tailoring to their perspective.

Below, this training based on the tailored consequences model is illustrated by presenting the experiences of two patients who participated in the group training: one of them, Anouk, with a beneficial outcome, and the other, Bernadette, with an unfavorable result.

Case 'Anouk'

Anouk is a 50-year-old married woman with an 11-year history of fibromyalgia. She receives full disability welfare. Nevertheless, she does a lot of voluntary work and she is a trainer in informal care.

Anouk grew up with a schizophrenic mother, to whom she could not express her emotions. She received inpatient mental treatment for an identity problem in 1993 and outpatient mental treatment for a depression in 1996.

After referral by her general practitioner, we invite Anouk to inform her about the training. Because of holidays, she cancels twice asking invariably for a new invitation.

After the third invitation, she arrives in a mobility scooter wearing braces around her wrists. After the interview, Anouk completes the *Structured Clinical Interview for DSM-IV Axis I Disorders/Patient edition* (SCID-I/P) [55] and the *Vragenlijst Kenmerken van Persoonlijkheid* (VKP) - self-report questionnaire for DSM-IV Axis II personality disorders based on the International Personality Disorder Examination (IPDE) [46]. The SCID-I/P shows a previous single episode depressive disorder and a pain disorder. The VKP indicates a paranoid and an obsessive-compulsive personality disorder.

Anouk's aim is "contributing to the training and research as an expert and trainer in informal care". She remarks spontaneously to the trainer: "I am so glad that you called it a training instead of a group therapy!"

In the sessions, Anouk shares her experiences freely, although she reports difficulty with being a trainee instead of a trainer. She realizes that her use of orthopedic devices and her busy day schedule have become harmful. She reduces her device use, builds in short breaks to recuperate and doesn't work on the computer after 8.00 pm anymore. Anouk misses the session on emotional consequences. She catches up on this subject when improving physical shape is introduced as a long-term beneficial survival strategy. Anouk expresses her anger towards the trainer. Anouk thinks that the trainer is wrong about the beneficial effect of improving one's physical shape. On physicians' advice in the past, Anouk has tried several times to improve her physical shape, which led to dramatic relapses and no support regarding these relapses by these physicians. The trainer validates her anger and also repeats the psycho-education on the beneficial physiological mechanism underneath the survival strategy of improving one's physical shape. In accordance with the training protocol, the trainer promises to weekly evaluate whether this survival strategy is also beneficial for Anouk's body. Anouk reports in the next session that she wants to improve her physical shape, albeit in a lower speed. Her courage is complimented. At the end of the training, Anouk does not use her braces or mobility scooter anymore. She enrolls herself for Nordic Walking classes and reports less symptoms and less sleeplessness. Anouk's evaluation of the training is: "My symptoms are definitely physical, but the cause of my symptoms is medically unexplained yet. This training recognizes patients are burdened and it is doing something for them. I did not want to miss the training for the world, even as an old stager. You always get something out of this training."

To quantify the outcome on quality of life, Anouk completes the *36-item Medical Outcomes Study Short-Form General Health Survey* (SF-36) before and after the group training. The SF-36 is a validated and reliable self-report questionnaire with 36 questions and standardized response choices for assessing quality of life. The quality of life is measured by eight multi-item scales: Physical functioning, Role functioning physical, Bodily pain, General health, Vitality, Social functioning, Role functioning emotional and Mental health. A higher score indicates a better quality of life.

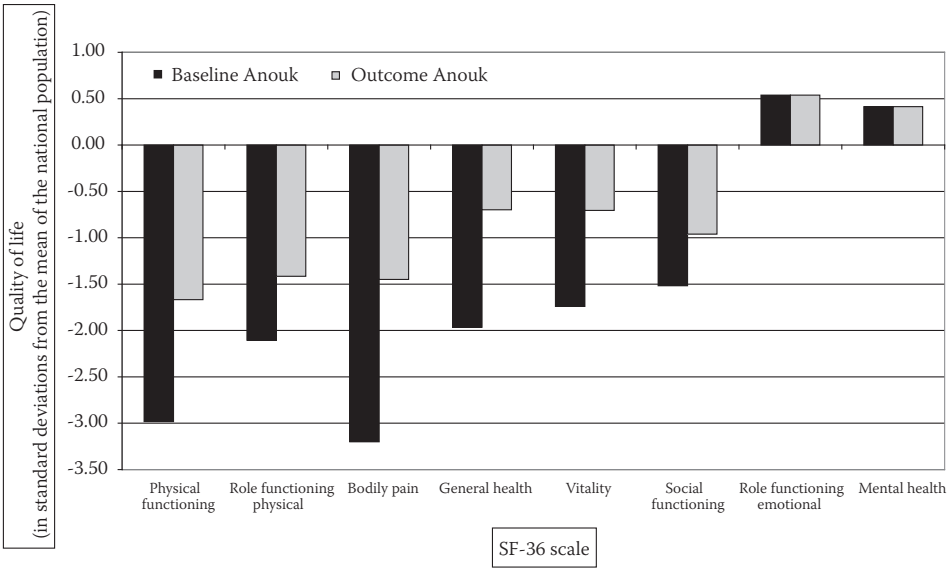


Figure 4.2. Anouk's quality of life before and after the group training in comparison with the general Dutch population

Figure 4.2 shows Anouk's quality of life in standard deviations from the mean found in the general Dutch population.

Case 'Bernadette'

Bernadette is a 26-year-old woman with a 10-year history of chronic fatigue. Her medical history shows glandular fever at the age of 16 years, after which her fatigue persists. In the same year, her mother left for another man, leaving Bernadette with her alcohol-addicted father. Now, Bernadette is married and works 32 hours weekly as a switchboard operator.

After referral by her general practitioner, we inform Bernadette about the training. After the interview, Bernadette completes the SCID-I/P and VKP. The SCID-I/P shows an undifferentiated somatoform disorder. The VKP indicates no personality disorder. Bernadette's aim for the training is "doing things despite my fatigue by spacing time appropriately".

Bernadette hides herself in the background. She misses the problem-solving session about defining goals and making her own survival strategies towards them. At the end of the training, she starts sharing her daily life. Bernadette evaluates the training as informative but not applicable to her because of her "busy day schedule".

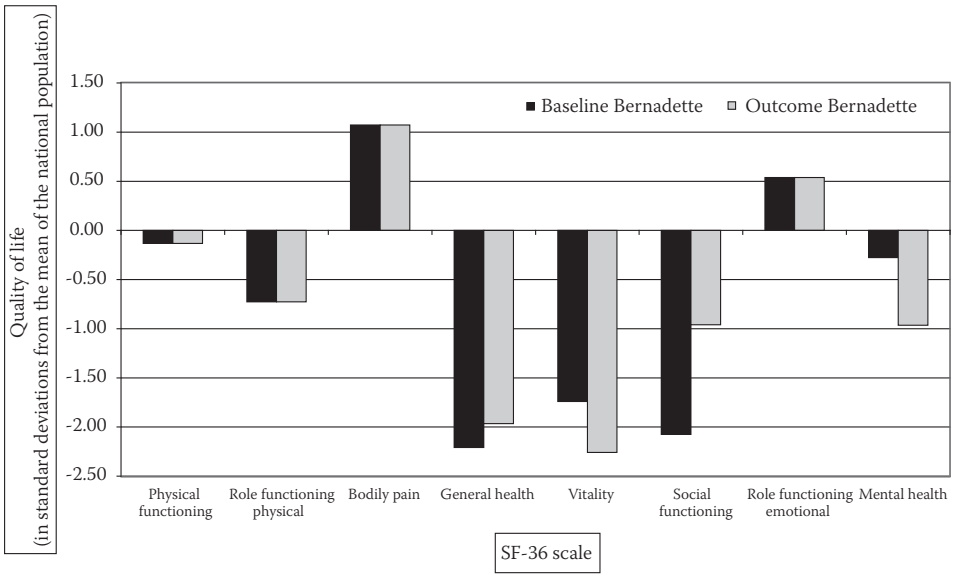


Figure 4.3. Bernadette's quality of life before and after the group training in comparison with the general Dutch population

To quantify the outcome on quality of life, Bernadette completes the SF-36 before and after the group training. Figure 4.3 shows Bernadette's quality of life in standard deviations from the mean found in the general Dutch population.

After the end of the group training, Bernadette asks the trainer for "an interview with a psychologist because of my anxiety anticipating the death of people around me. I am tired due to too much ruminating about awful things and I puzzled my head off". We arrange psychotherapy, in which she engages.

Discussion

We tailored the consequences model to our assumption that patients have a physical perspective of their symptoms by approaching the consequences model bottom-up (starting with consequences and unconditionally accepting and justifying their existence) instead of top-down (starting with addressing irrational beliefs and disputing them). Our assumption that patients in primary care have a physical perspective seems to be supported by the two patients presented, who report their suffering on the SF-36 typically in physical terms. Also, Anouk's spontaneous remarks ("I am so glad that you called it a training instead of a group therapy!" and "My symptoms are definitely physical, ..") show preference for physical terms.

Our assumption about patients' physical perspective can be tuned by recent research. Peters et al. [120] found that patients use a multifaceted explanatory model, which

includes both physical and psychosocial factors, and the interaction between them. Sumathipala et al. [154] showed that the explanatory model of non-Western patients is non-specific. In this study, 56% of the patients could not offer a specific cause for their UPS. Dwamena et al. [47] and Schweickhardt et al. [129] concluded that the explanatory model of patients with UPS in primary care differs between significant understanding of psychological factors that influence UPS and much lesser psychological insight. They classified the majority of the patients as having less psychological insight. Even if patients have a multifaceted explanatory model, they prefer to communicate about the physical factors [120]. Therefore, our assumption that patients in primary care formulate their complaints in terms of physical problems seems to hold. The best chance that patients accept a treatment is by tailoring it to their physical perspective.

To take this initial acceptance to the next level, a match between patients' and trainings' goals must be established. As well as in patients using a multifaceted explanatory model [120], as in patients with less psychological insight [47], as in common patients with UPS [113], support is the most highly valued goal by patients. In the tailored consequences model, the bottom-up approach provides a high amount of support. By justifying patients' reactions to their UPS because of its benefits in short term, patients are relieved from blame, supported in their reactions to cope and trusted that they can use even more sophisticated reactions to improve their quality of life. Because support and relief from being blamed are also common factors that facilitate the development of a working alliance, the likelihood of beneficial effects of the bottom-up approach is increased [91]. All in all, this approach seems promising for the working alliance.

Anouk seems to bond easily with the trainer, allowing even a self-disclosure about her difficulties of being a trainee. However, expressing her anger towards her trainer must have been difficult, because, in her childhood, expression of emotions was not tolerated. But, as her anger is unconditionally accepted, the opportunity comes up to negotiate further about goals and tasks. In other words, a working alliance can be more firmly established. As Anouk has a paranoid and obsessive-compulsive personality disorder, this is even more striking.

Bernadette has difficulties with being prominent, let alone to bond with her trainer. This is not surprising, as, at the age of 16 years, her mother left her, just when she was individuating. By this, individuating might be associated with abandonment by others. Her increased participation in the group may reflect an increased faith in being accepted. Her reported anxiety concerning the possible death of loved ones suggests that she still questions the unconditionality of acceptance. Although the working alliance is still too premature for stable beneficial changes, it is sufficient to start psychotherapy.

Our group training seems to match the -by patients most frequently communicated- perspective of UPS and patients' goal for management of their UPS. This facilitates working alliances, even when the childhood experiences with bonding are unfavorable.

Working alliances robustly predict beneficial therapy outcome [91]. A randomized controlled trial is ongoing to explore if the group training is indeed as promising as it seems to be.

Chapter 5

Bevorderen van gepaste zorg voor patiënten met onverklaarde lichamelijke klachten: een voorbeeld

Samenvatting

Onverklaarde lichamelijke klachten komen vaak voor. Als deze klachten voldoen aan de DSM-IV-R criteria van een somatoforme stoornis, dan is de kans op een spontaan herstel klein, is de kwaliteit van leven laag en zijn de kosten hoog. Cognitieve gedragstherapie blijkt deze klachten te kunnen verminderen, de kwaliteit van leven te verhogen en kosten te verlagen. Individuele cognitieve gedragstherapie gebaseerd op het 'gevolgenmodel' is effectief gebleken in de tweedelijns medische gezondheidszorg. Een laagdrempelige inzet ervan door de huisarts werd echter gehinderd vanwege de lage acceptatie door patiënten en het verlies van effectiviteit in de eerste lijn. In deze casusbeschrijving presenteren wij een modificatie van het gevolgenmodel, waarin het creëren van een laagdrempelig en effectief aanbod, dat door de GZ-psycholoog kan worden ingezet, centraal staat.

Inleiding

In één van de zes consulten bij de huisarts is er sprake van onverklaarde lichamelijke klachten, die geclassificeerd kunnen worden als een somatoforme stoornis [38]. De meest voorkomende somatoforme stoornissen zijn ongedifferentieerde somatoforme stoornis met een prevalentie van 13% en chronisch pijnstoornis met een prevalentie van 1.6% [38]. Slechts 25% van de somatoforme stoornissen verdwijnt spontaan [11]. Deze klachten leiden tot een lage kwaliteit van leven [42; 79; 135] en hoge maatschappelijke [124] en medische [14] kosten. Cognitieve gedragstherapie blijkt deze klachten te kunnen verminderen, de kwaliteit van leven te verbeteren en de kosten te verlagen [86; 111; 152]. In Nederland wordt in de psychologische behandelprotocollen voor onverklaarde lichamelijke klachten [141; 163] vooral het gevolgenmodel aanbevolen. De rationale van het gevolgenmodel is dat onverklaarde lichamelijke klachten tot automatische gedachten leiden, zowel over de oorzaak van deze klachten als over de manier hoe ermee om te gaan [141]. Deze automatische gedachten hebben gevolgen, die klachten kunnen verminderen, maar ze ook in stand kunnen houden of verergeren. Een behandelaanbod op basis van dit model had in een universitaire polikliniek Interne Geneeskunde een hoge acceptatie: 81% van de patiënten accepteerde dit aanbod [142]. Als een behandelaanbod met dezelfde rationale echter bij de huisarts werd aangeboden, dan bleek een individueel aanbod niet effectief [9] en kon een groepsaanbod niet worden opgestart omdat slechts 5% van de patiënten het accepteerde [12]. Omdat de capaciteit van de tweede lijn beperkt is, de tweede lijn minder toegankelijk is en naar schatting zo'n 50 tot 80% van de patiënten met onverklaarde klachten überhaupt een verwijzing naar de geestelijke gezondheidszorg niet opvolgt [5], is een aanbod in een eerstelijns medische setting zinvol. De vraag is dan of het gevolgenmodel gemodificeerd kan worden om een laagdrempelig en effectief aanbod te creëren dat toepasbaar is in de eerste lijn. Aan de hand van de onderstaande casus beantwoorden we deze vraag.

Casus 'Carel'

Carel heeft al 2 jaar chronische darm- en buikklachten, die met het Gestructureerd Klinisch Interview voor de vaststelling van DSM-IV As I stoornissen/Patiënten editie (SCID-I/P) [55] als ongedifferentieerde somatoforme stoornis worden geclassificeerd. De klachten begonnen met korte periodes, waarin bepaalde etenswaren tot diarree leidden. Geleidelijk raakte hij na elke warme maaltijd aan de diarree en had hij ondraaglijke buikpijn. Hierop is Carel alleen wit brood op wisselende tijden gaan eten, waarna zijn diarree-klachten veranderden in obstipatie-klachten. Hij gebruikt nu een laxeermiddel en vitamine-preparaten. Carel komt regelmatig bij de huisarts, want zijn klachten maken zijn leven "niet leefbaar".

Carel is een 40-jarige gehuwde vader van drie zonen. Hij werkt fulltime als accountant en doet zijn werkzaamheden nu voornamelijk vanuit huis. Voorheen ging hij laat naar bed en werd doorgaans wakker vóór de wekker afging. Nu gaat hij 's avonds om half tien naar bed en wordt door de wekker gewekt. Hij slaapt regelmatig overdag. Hij heeft weinig energie voor sociale contacten en zijn hobby's. Hij blijft vaak thuis als zijn echtgenote naar een verjaardag gaat. Door zijn onregelmatige eetpatroon eet hij niet meer met zijn gezin mee. Hij is gestopt met hardlopen.

In het medisch onderzoek naar zijn darm- en buikklachten komen geen bijzonderheden naar voren. Vijf jaar geleden heeft hij een rugoperatie gehad, waardoor hij negen maanden niet kon werken.

Carel is nooit in behandeling geweest bij een geestelijke gezondheidszorginstelling. Hij benadrukt met klem, dat zijn klachten "niet tussen de oren zitten".

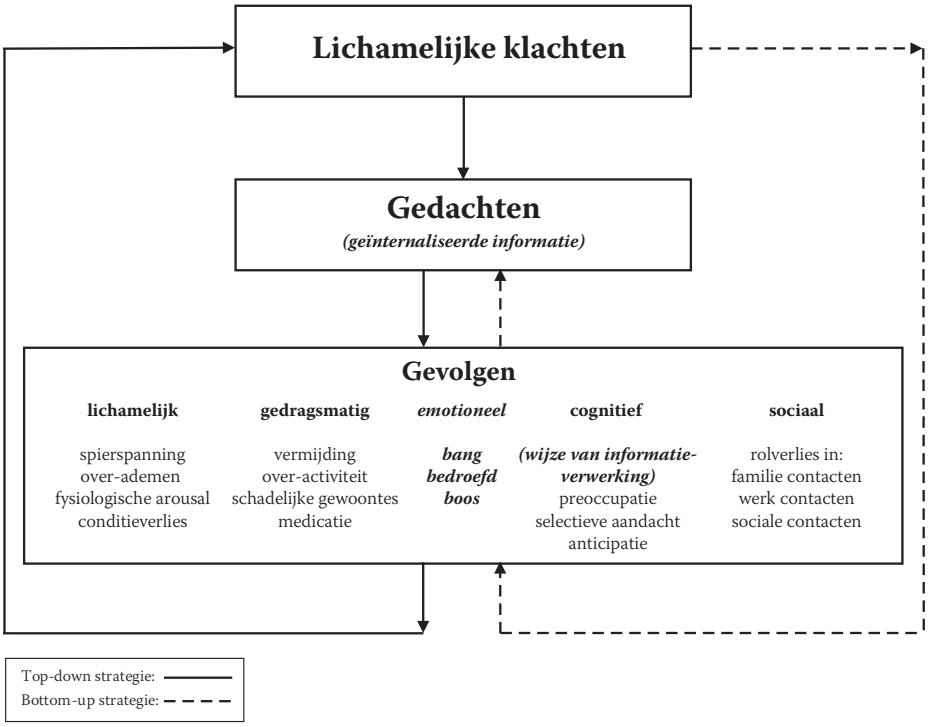
Drempels verlagen: hoe?

Het oorspronkelijke gevolgenmodel [140; 141] (Figuur 5.1: getrokken pijlen) gaat ervan uit, dat:

- er *eerst* gedachten over de lichamelijke klachten en coping ontstaan;
- deze gedachten *daarna* leiden tot lichamelijke, gedragsmatige, cognitieve en sociale gevolgen;
- deze gevolgen *vervolgens* de lichamelijke klachten verergeren of *in stand houden*.

Samenvattend, de patiënt doorloopt het gevolgenmodel van boven naar beneden (*top-down*). Dit model is voor psychologen uitgewerkt in een individueel behandelaanbod [141], dat als doel heeft het verminderen van de gevolgen van lichamelijke klachten om zo sneller te *herstellen*.

Carel zou moeite kunnen hebben met een behandelaanbod, dat zich baseert op dit model. Ten eerste sluit het model niet aan bij het natuurlijke verloop van zijn klachten. Carel had eerst darmklachten, waarop zijn lichaam begon te reageren met pijn en wellicht met wrijven over zijn buik. Toen zijn klachten bleven voortduren, zijn er gedachten ontstaan over zijn klachten en hoe ermee om te gaan. Ten tweede zou Carel het idee kunnen krijgen, dat niet zijn lichaam maar zijn psyche het probleem is door te beginnen met zijn gedachten in reactie op zijn lichamelijke klachten. Hij kan de indruk krijgen dat men denkt dat zijn klachten "tussen zijn oren zitten". Dit sluit niet aan bij het fysieke perspectief van patiënten met onverklaarde lichamelijke klachten, die hun klachten vaker dan patiënten met verklaarde lichamelijke klachten toeschrijven aan fysieke oorzaken [112]. Ten derde kan Carel het aanbod afwijzen vanwege de impliciete suggestie dat hij schuldig zou zijn aan het voortduren van zijn klachten. Als hij anders zou denken en doen, zou er herstel zijn opgetreden. Tot slot zou Carel het aanbod kunnen afwijzen,



Figuur 5.1. Het *gemodificeerd* gevolgenmodel

omdat een individueel aanbod hem het idee geeft uitzonderlijk c.q. 'gek' te zijn en ook het gebruik van het woord "behandeling" suggereert pathologie.

Als het gevolgenmodel meer zou aansluiten bij zijn fysieke perspectief op de klachten, hem niet verantwoordelijk maakt voor het hebben en óók niet voor het voortduren van de klachten (ontschuldiging) en hem niet pathologiseert, dan zou dit een laagdrempelig aanbod voor Carel opleveren. Dit kan gerealiseerd worden met de volgende modificaties van het gevolgenmodel (Figuur 5.1: gestippelde pijlen):

1. Bottom-up in plaats van top-down

Het gemodificeerd model begint met lichamelijke gevolgen (bottom-up) in plaats van met gedachten (top-down). Deze modificatie sluit beter aan bij het natuurlijk verloop van klachten en voorkomt de suggestie van "tussen de oren zitten". In tweede instantie kan het gemodificeerd gevolgenmodel van boven naar beneden worden doorlopen. Overigens bleek uit onderzoek bij depressie en angst, dat gedragsmatige interventies voldoende zijn om klachten te verminderen en dat cognitieve interventies geen meerwaarde hebben [97].

2. Verergerende in plaats van instandhoudende factoren

Het gemodificeerd model labelt de gevolgen alleen als verergerende factoren en niet als instandhoudende factoren. Deze modificatie houdt consequenter vast aan het idee dat oorzaken onbekend zijn en voorkomt een beschuldiging naar patiënten over het voortduren van de klachten.

3. Cursusdoel 'verbeteren van kwaliteit van leven' in plaats van behandeldoel 'herstellen'

Voortvloeiend uit punt 2, het gemodificeerd gevolgenmodel heeft als doel het verbeteren van kwaliteit van leven ondanks de klachten in plaats van herstel.

4. Groepsaanbod in plaats van individueel aanbod

Het gemodificeerd model is uitgewerkt in een groepscursus in plaats van een individuele behandeling. Een aanbod in een groep leidt tot onderlinge herkenning, waardoor de klachten en gevolgen worden genormaliseerd. Ook het gebruik van het woord 'cursus' is neutraal en hierdoor normaliserend.

Het gemodificeerd gevolgenmodel [172] gaat dus van het volgende uit, dat:

- er *eerst* lichamelijke, gedragsmatige, emotionele, cognitieve en sociale gevolgen ontstaan in reactie op de lichamelijke klachten;
- deze gevolgen leiden *daarna* tot gedachten;
- de gevolgen *vervolgens* –al of niet mede ontstaan in reactie op gedachten– de lichamelijke klachten *verergeren*.

Samenvattend, de patiënt doorloopt het gevolgenmodel eerst van beneden naar boven (*bottom-up*). Dit model is uitgewerkt voor GZ-psychologen in een groepsaanbod in de vorm van de cursus 'Omgaan met de *gevolgen* van onverklaarde lichamelijk klachten' [170], die als doel heeft het verbeteren van de *kwaliteit van leven*.

De cursus 'Omgaan met de *gevolgen* van onverklaarde lichamelijk klachten' omvat 13 wekelijkse bijeenkomsten van ieder twee uur. Alle bijeenkomsten, met uitzondering van de eerste bijeenkomst, hebben de volgende opbouw:

- het delen van de ervaringen van de afgelopen week;
- het bespreken van het (t)huiswerk;
- het doen van een ademhalings- en ontspanningsoefening;
- het identificeren en vervangen van overlevingsstrategieën die op korte termijn helpend zijn geweest en op lange termijn niet-helpend zijn geworden;
- het samenvatten van de bijeenkomst en introduceren van het nieuwe (t)huiswerk.

Tabel 5.1. Het programma van de cursus per bijeenkomst

Bijeenkomst	Programma	
	Kennismaking	
1	Plenair bespreken van eigen cursusdoelen en lichamelijke klachten	
	Gevolgen	**Overlevingsstrategieën**
2	Lichamelijke	Stoppen van de fysiologische arousal en spierspanning en vervangen door de ademhalings- en ontspanningsoefening [109; 115; 164]
	Gedragsmatige	Stoppen van niet-helpende automatismen en vervangen door onverenigbare handelingen [70]
3	Gedragsmatige	Stoppen van de onder- en/of overactiviteit en vervangen door het afwisselen van activiteiten en het inplannen van pauzes door de activiteitenplanner [141]
4	Emotionele	Stoppen van de fysiologische arousal van emoties en vervangen door de ademhalings- en ontspanningsoefening [109; 115; 164]
		Herkennen van emotionele gevolgen als belangrijk signaal dat: -de situatie niet overeenkomt met eigen wensen, behoeften, verwachtingen -de situatie om verandering vraagt
5	Gedachten	Stoppen van de niet-helpende en niet-passende gedachten en vervangen door helpende en passende gedachten met een 4G-schema (Gebeurtenis → Gedachten → Gevoel → Gedrag) [22; 41]
6	Lichamelijke	Verhogen van de lichamelijke conditie op geleide van tijd [141]
7	Cognitieve	Stoppen van de niet-helpende informatieverwerking en vervangen door helpende informatieverwerking [158]
	Sociale	Inventariseren en samenvatten van alle gevolgen in het gemodificeerd gevolgenmodel
		Bespreken van dit persoonlijke gevolgenmodel met een vertrouwenspersoon
8-12	Diverse	Bedenken van passende overlevingsstrategieën om kwaliteit van leven te verbeteren door: -het bewust worden en definiëren van problemen die kwaliteit van leven verminderen -het bedenken, kiezen, uitvoeren en evalueren van overlevingsstrategieën om kwaliteit van leven te verhogen [110; 158]
	Terugvalpreventie	
13	EHBO-koffer voor kwaliteit van leven samenstellen uit aangereikte overlevingsstrategieën om een terugval te voorkomen	
Follow-up	Evaluatie van de kwaliteit van leven met de onderstaande vragen: 1. Hoe heb je je kwaliteit van leven kunnen vasthouden of zelfs kunnen verhogen? 2. Welke handvatten gebruik je hiervoor? 3. Heb je je doel kunnen bereiken?	

Na drie maanden vindt er een follow-up bijeenkomst plaats. Tabel 5.1 geeft het programma van de cursus per bijeenkomst weer.

Deze cursus werd geïmplementeerd als anderhalve lijnszorg door vanuit een Riagg de samenwerking met voornamelijk eerstelijns medische instellingen te zoeken. De cursussen werden vervolgens georganiseerd in deze instellingen (huisartsenpraktijk, GGD, apotheek, polikliniek van een ziekenhuis). 'Anderhalve lijnszorg' verlaagt de drempel van een Riagg, omdat cursussen de capaciteit van een Riagg vergroten, cursussen

een beperkte indicatiestelling vragen en een verwijzing naar een cursus in een medische setting meer aansluit bij het perspectief van patiënten op hun klachten.

Vervolg casus 'Carel'

Op verwijzing van zijn huisarts neemt Carel deel aan de cursus, waarvan hij 10 van de 13 bijeenkomsten volgt. Zijn cursusdoelen zijn "handvatten om een leefbaar leven te hebben".

Carel voelt zich snel rustiger door de ademhalings- en ontspanningsoefening. Hij bemerkt dat hij een laag activiteitenniveau heeft. Zijn activiteiten nemen toe, waarna hij zijn conditie wil opbouwen door weer te gaan hardlopen met zijn vriendengroep. Zijn enthousiasme wordt geprezen, maar een geleidelijke opbouw wordt geadviseerd. Carel is vastberaden en gaat toch hardlopen, waarna hij triomfantelijk meldt dat hij 'alleen gewone spierpijn' heeft. Ook zijn activiteiten op het werk nemen toe, waardoor hij weer klanten bezoekt. Zijn fysieke perspectief blijkt uit zijn reactie op een medecursiste, die een antidepressivum gebruikt en zichzelf hierdoor als persoon zwak ervaart. Carel 'ontschuldigt' deze cursiste door depressie als een biologisch in plaats van een psychologisch fenomeen te beschrijven. Carel bedenkt overlevingsstrategieën om meer tijd door te brengen met zijn gezin, door wie hij zich nu buitengesloten voelt en van wie hij zich afsluit door veelvuldig op zijn werkkamer te zijn. Eén van zijn overlevingsstrategieën is samen eten met zijn gezin. Het valt hem dan op, dat zijn zonen hem nu wel in hun verhalen betrekken en dat hij zelf ook het gesprek aan tafel kan sturen. Carel gaat regelmatiger eten en leven, neemt meer pauzes en loopt weer tweemaal in de week hard met zijn vriendengroep. Zijn EHBO-koffer vult hij met de overlevingsstrategie 'het gesprek met mijn gezin continueren'. In de follow-up bijeenkomst blijkt Carel een nieuwe functie bij een andere werkgever te hebben. In zijn nieuwe functie heeft hij minder verantwoordelijkheid en werkt hij minder uren. Dit geeft hem meer tijd voor zichzelf en zijn gezin dat voor hem 'ruimschoots het verlies van inkomsten compenseert'.

Drempels verlagen: werkt het?

Met name artsen verwezen patiënten naar de cursus. Slechts 18% van de verwijzingen kwam vanuit de geestelijke gezondheidszorg. Zo'n 71% van de verwezen patiënten volgde hun verwijzing op, ruim meer dan het eerder geschatte aantal opgevolgde verwijzingen van slechts 20 tot 50% [5]. Hierdoor kon de cursus ook daadwerkelijk starten en de effectiviteit ervan onderzocht worden. Een eerder groepsaanbod in de eerste lijn op basis van het oorspronkelijke gevolgenmodel bleek niet uitvoerbaar door een te klein aantal patiënten [12].

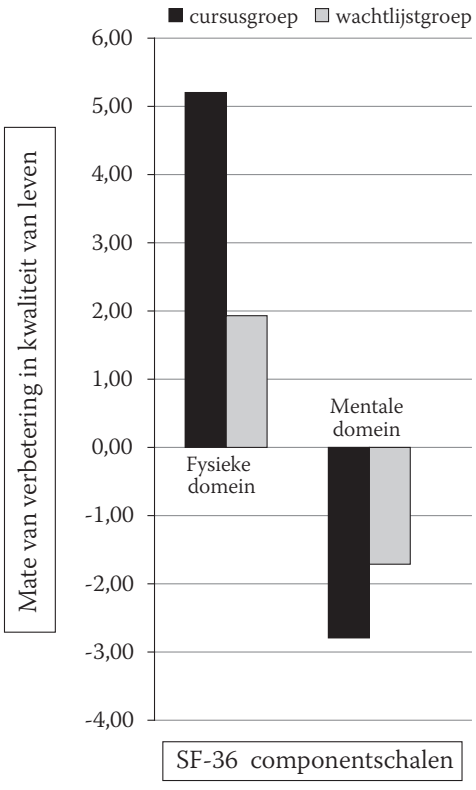
Tabel 5.2. Kenmerken van de onderzochte patiëntengroep

Sociodemografische kenmerken	**Cursus (n=84)**	**Wachtlijst (n=78)**
Geslacht		
vrouw	67	64
man	17	14
Leeftijd in jaren, gemiddelde *(interkwartiel range)*	46 *(38-53)*	44 *(35-52)*
Nationaliteit		
Nederlands	72	69
anders	12	9
Burgerlijke staat		
gehuwd of samenwonend	62	48
anders	22	30
Opleidingsniveau		
basisonderwijs of minder	7	7
lager beroepsonderwijs of MAVO	29	25
middelbaar beroepsonderwijs of HAVO	33	24
hoger beroepsonderwijs, VWO of WO	15	21
onbekend	0	1
Werk		
werk	29	28
geen werk	55	50
Verwijzer		
eerstelijns medische gezondheidszorg	41	41
tweedelijns medische gezondheidszorg	28	23
tweedelijns geestelijke gezondheidszorg	15	14
Kenmerken van Onverklaarde Lichamelijke Klachten (OLK)		
Duur van OLK in jaren, mediaan *(interkwartiel range)*	8 *(3-16)*	9.5 *(3-17)*
Classificatie van OLK gemeten door SCID-I/P		
ongedifferentieerde somatoforme stoornis	32	31
chronische pijnstoornis	52	47
Comorbide DSM-IV stoornissen		
Comorbide DSM-IV As I classificaties gemeten door SCID-I/P		
stemmingsstoornis (lifetime)	13 (40)	11 (30)
angststoornis (lifetime)	20 (36)	27 (41)
aan middelen gebonden stoornis (lifetime)	1 (12)	0 (6)
eetstoornis (lifetime)	1 (4)	0 (2)
psychotische stoornis (lifetime)	0 (0)	0 (1)
somatisatie stoornis	14	10
hypochondrie	1	1
aanpassingsstoornis	2	2

Tabel 5.2. Kenmerken van de onderzochte patiëntengroep *(vervolg)*

Comorbide DSM-IV As II stoornis gemeten door VKP		
paranoïde persoonlijkheidsstoornis	6	12
schizoïde persoonlijkheidsstoornis	2	3
schizotypische persoonlijkheidsstoornis	1	1
anti-sociale persoonlijkheidsstoornis	0	1
borderline persoonlijkheidsstoornis	2	5
theatrale persoonlijkheidsstoornis	1	1
narcistische persoonlijkheidsstoornis	0	2
ontwijkende persoonlijkheidsstoornis	15	14
afhankelijke persoonlijkheidsstoornis	2	2
obsessieve-compulsieve persoonlijkheidsstoornis	14	10
Gemiddeld aantal bevestigde DSM-IV As II criteria gemeten door VKP	16	14

De effectiviteit van de cursus is onderzocht in een experiment met een voor- en nameting [173]. De belangrijkste uitkomstmaat was de kwaliteit van leven, die gemeten werd met de twee componentschalen (fysiek en mentaal) van de zelfrapportage vragenlijst SF-36 [167]. De fysieke componentschaal meet de kwaliteit van leven in het



Figuur 5.2. Effectiviteit van de cursus

fysieke domein en de mentale componentschaal meet deze in het mentale domein. Beide schalen zijn zo geconstrueerd, dat ze een gemiddelde van 50 hebben in de algemene populatie, met een standaardafwijking van 10.

Voor het experiment werden 162 patiënten met onverklaarde lichamelijke klachten, die voldeden aan de DSM-IV criteria van ongedifferentieerde somatoforme stoornis of van chronisch pijnstoornis, gerandomiseerd naar de cursus of naar een wachtlijst. Bij de voormeting verschilden de cursus- en wachtlijstgroep niet significant van elkaar op de sociodemografische en klinische kenmerken, die in Tabel 5.2 staan.

Opvallend in de voormeting van de kwaliteit van leven waren de lage gemiddelden in het fysieke domein (cursusgroep=29.3; wachtlijstgroep=29.1) en de relatief hoge gemiddelden in het mentale domein (cursusgroep=43.7; wachtlijstgroep= 46.7). Dit betekent dat patiënten hun kwaliteit van leven in het fysieke domein als slechter evalueerden dan die in het mentale domein.

De veranderingen in de kwaliteit van leven van de cursusgroep werden vergeleken met de veranderingen in de wachtlijstgroep (Figuur 5.2). De cursusgroep rapporteerde een significant grotere verbetering van hun kwaliteit van leven in het fysieke domein dan de wachtlijstgroep (p=0.003). De gemiddelde scores van de kwaliteit van leven in het mentale domein bleven relatief hoog (cursusgroep=46.5; wachtlijstgroep=45.1) en de veranderingen hierin waren niet significant (p=0.35). De wachtlijstgroep kon na de nameting deelnemen aan de cursus. Na de cursus werden patiënten een jaar gevolgd, waarin er geen significante terugval van de kwaliteit van leven in het fysieke domein werd gezien (p=0.72).

De effectiviteit van de cursus zou afwijkend kunnen zijn voor patiënten met comorbide stoornissen in het heden en/of het verleden op DSM-IV As I en/of II. Overeenkomstig met resultaten uit eerdere onderzoeken [19; 95; 107; 121] bleken patiënten met comorbide psychiatrische stoornissen echter evenveel te profiteren als patiënten zonder deze stoornissen. Drempels verhogen door indicatiestelling en vervolgens het uitsluiten van patiënten met deze comorbide stoornissen lijkt daarom zinloos en onnodig patiënten van een effectieve behandeling te onthouden.

Conclusie

De -in dit artikel voorgestelde- modificatie van het gevolgenmodel heeft tot een laagdrempelige en effectieve cursus voor patiënten met onverklaarde lichamelijke klachten geleid. GZ-psychologen kunnen deze cursus als anderhalve lijnszorg in een medische setting uitrollen om de beschikbaarheid ervan voor patiënten te vergroten.

Chapter 6

Effective group training for patients with unexplained physical symptoms: a randomized controlled trial with a non-randomized one-year follow-up

Abstract

Background

Although cognitive-behavioral therapy for Unexplained Physical Symptoms (UPS) is effective in secondary care, studies done in primary care produced implementation problems and conflicting results. We evaluated the effectiveness of a cognitive-behavioral group training tailored to primary care patients and provided by a secondary community mental health service reaching out into primary care.

Methodology/Principal findings

The effectiveness of the group training was explored in a randomized controlled trial. In this trial, 162 patients with UPS classified as undifferentiated somatoform disorder or as chronic pain disorder were randomized either to the training or to a waiting list. Both lasted 13 weeks. The preservation of the training's effect was analyzed in non-randomized follow-ups, for which the waiting group started the training after the waiting period. All patients who attended the training were followed-up after three months and again after one year.

The primary outcomes were the physical and the mental summary scales of the SF-36. Secondary outcomes were the other SF-36-scales and the SCL-90-R. The development of the training's effects in the randomized controlled trial and the follow-ups was analyzed with linear mixed modeling.

In the randomized controlled trial, the training had a significantly positive effect on the quality of life in the physical domain (Cohen's d=0.38; p=0.002), but this overall effect was not found in the mental domain. Regarding the secondary outcomes, the training resulted in reporting an improved physical (Cohen's d=0.43; p=0.01), emotional (Cohen's d=0.44; p=0.01), and social (Cohen's d=0.36; p=0.01) functioning, less pain and better functioning despite pain (Cohen's d=0.51; p=<0.001), more vitality (Cohen's d=0.30; p=0.05), less physical symptoms (Cohen's d=-.23; p=0.05) and less sleep difficulties (Cohen's d=-0.25; p=0.04) than time in the waiting group. During the non-randomized follow-ups, there were no relapses.

Conclusions/Significance

The cognitive-behavioral group training tailored to patients with UPS in primary care and provided by an outreaching secondary mental health service appears to be effective and to broaden the accessibility of treatment for UPS.

Introduction

The estimated prevalence of Unexplained Physical Symptoms (UPS) ranges from 18 to 74% in primary care [34; 43; 75], and from 30 to 52% in secondary care [73; 97; 107; 139]. UPS is more prevalent in women than in men [13; 97; 117; 143] and women in their forty's seem to run a higher risk [34; 117]. Other sociodemographic characteristics seem not to be associated with UPS in a consistent manner. For example, some studies found lower socioeconomic background to be associated with UPS [13; 143], while others found an association with having work and a higher education attainment [97]. Patients with UPS attribute their physical symptoms more to physical causes than to lifestyle factors in comparison to patients with a medical diagnosis [97]. Moreover, patients with UPS are more reluctant than patients with mental disorders to accept a psychiatric diagnosis for their symptoms [77]. UPS is associated with more concomitant psychological symptoms, more impaired functioning and higher medical utilization than other patient groups [13; 37; 117].

Cognitive-behavioral therapy has shown to be most effective for patients with UPS. It reduces UPS and concomitant psychological symptoms, improves daily functioning, and reduces financial expenses [76; 96; 130] without causing harmful effects [57]. However, the effect of this treatment has been studied mainly in medical subspecialty clinics or mental health centers [4; 76; 106] – resources that are not easily accessible to patients [32], either because their capacity is limited, or because patients refuse to be referred to the mental health services [5; 106].

To make treatment for UPS more accessible to patients, general practitioners have been trained to carry out cognitive-behavioral therapy. However, only two studies have shown effect when this therapy was provided by general practitioners [15; 82]; most other studies were unable to show any conclusive effect [3; 8; 90; 109; 131; 134]. Also, the transfer of this therapy by general practitioners into routine clinical practice has been hampered by practical issues at the level of the general practitioner, the patients and the treatment. At the level of general practitioners, the implementation was difficult as they hesitated to implement this treatment for UPS. In a British study [111], 1,934 general practitioners were invited to be trained in cognitive-behavioral therapy. Despite the promise of financial compensation, only 70 agreed to participate (3.6%). Those who did participate reported difficulties in implementing the therapy in their family practice because of, for example, the limited time available in patient-physician encounters [38]. At patient's level, the implementation was difficult as patients with UPS hesitated to disclose psychosocial issues to their general practitioners [104], and they were less satisfied about the quality of care from their general practitioners than patients with a medical diagnosis. For example, patients with UPS felt that their general practitioner did not take them seriously and took too little time for them [35; 37]. At treatment level,

the implementation was difficult as general practitioners and patients had different objectives for their encounters: the former aimed to explain and alleviate symptoms, while the latter hoped to find clinician's support [98; 104].

As an alternative to training general practitioners to carry out cognitive-behavioral therapy for UPS, it might be possible for professional therapists from a secondary community mental health service to make this therapy easily accessible to primary-care patients. First, however, three problems should be resolved: the capacity of secondary care should be increased, patients' refusal to be referred to mental health services should be reduced, and therapists' and patients' goals for treatment encounters should be aligned.

As a secondary community mental health service, we approached these problems as follows. First, to increase capacity, we organized group treatment instead of individual treatments. Second, to minimize patients' refusal to be referred to mental health services, we sought close collaboration with medical services and offered treatment locally at their centers. Moreover, we used a cognitive-behavioral model which had previously achieved high acceptance in a secondary medical outpatient clinic [123]. As the available manuals based on this model were only intended for individual treatments [122; 140; 141], we had to write a manual for group treatment [148]. Third, to align the goals of therapists and patients, we tailored the treatment to match primary-care patients' goals for treatment.

Objectives

Our first objective was to evaluate the effectiveness of the cognitive-behavioral group training tailored to primary care patients and provided by a secondary community mental health service reaching out into primary care. The second objective was to observe whether the effect of this group training was preserved in a one-year follow-up period. Our hypotheses were that the group training could raise the quality of life in patients with UPS, and that this effect could be preserved during the follow-up period.

Methods

The study protocol of this trial can be found in Chapter 3 and has been published elsewhere [173]. The CONSORT checklist is available as supporting information in Appendix B.

Ethics

The study was approved by the Erasmus Medical Research Ethics Committee and was registered in the Dutch Trial Register (NTR 1609) [149]. Patients in this study gave written informed consent.

Study design

The effectiveness of the group training was investigated in a randomized controlled trial. To this end, patients were randomized either to the training or to a waiting list after they had completed the baseline measurement (T_0). The second measurement (T_1) was made directly after the training (13 weeks), or after the same period for those on the waiting list.

The preservation of the effect of the group training was investigated in a non-randomized one-year follow-up. To this end, patients who had been randomized to the waiting list and had waited started the training after their second measurement (T_1). Patients who attended the training directly after randomization or after the waiting period were followed-up three months after the end of their treatment (T_2), and again one year after the end of their treatment (T_3).

Participants

General practitioners and specialists were asked to refer patients aged between 18 and 65 years whose physical symptoms, according to their clinical judgment, could not be fully explained by a known medical condition.

Patients were included if they signed the informed consent, and if their UPS fulfilled the DSM-IV criteria for an undifferentiated somatoform disorder or a chronic pain disorder. To verify whether the UPS fulfilled the criteria for undifferentiated somatoform disorder or chronic pain disorder, we used the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I/P) [48], a semi-structured validated interview for making the major DSM-IV Axis I diagnoses.

Patients were excluded from the study if poor language skills or handicaps, such as cognitive impairment, prevented them from understanding the training.

Interventions

The intervention is a cognitive-behavioral therapy based on the consequences model. In Figure 6.1, the consequences model is drawn with solid arrows [121]. In the consequences model, psychological and social factors, which are commonly labeled as causes [114], are labeled as consequences of UPS. UPS (such as abdominal pain) in itself is seen as a stressful condition about which patients develop dysfunctional beliefs (such as 'I have colon cancer') that produce cognitive, behavioral, physical, and social consequences. In the short term, these consequences have beneficial effects, either by themselves (such as eating easily digestible food to recuperate), or through interaction with other consequences (such as continuing an activity to distract oneself from the abdominal pain). In the long term, however, these consequences might produce self-perpetuating vicious circles that maintain or aggravate UPS (such as eating less and less, and continuing an activity beyond one's physical limits that leads to more abdominal pain

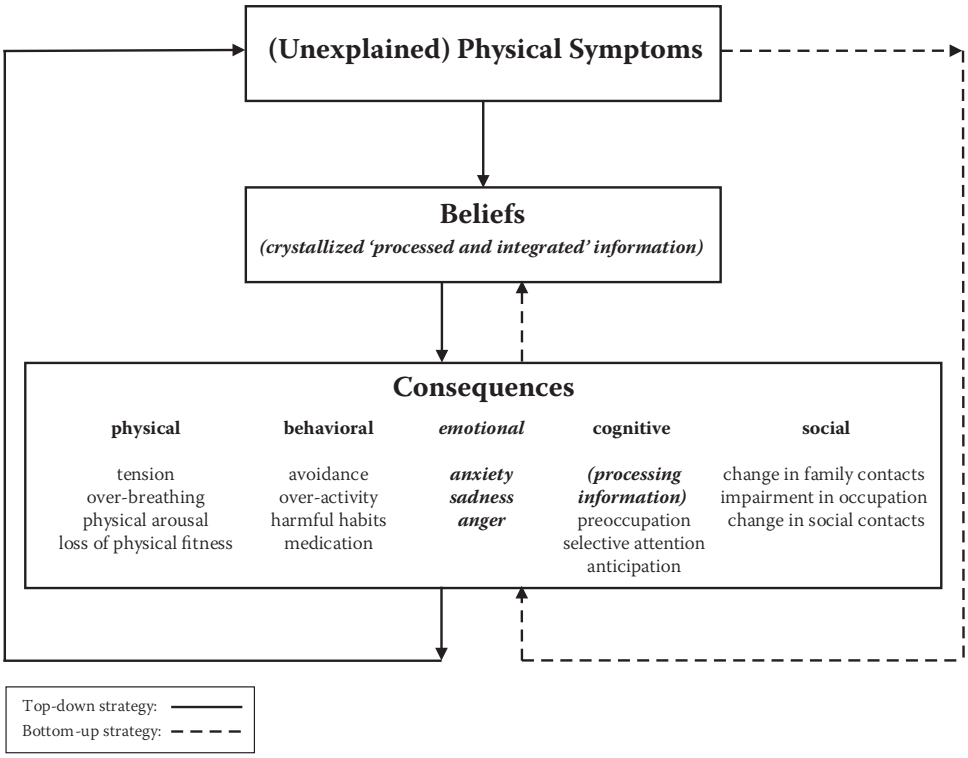


Figure 6.1. The *tailored* consequences model

and tiredness). The goal of a treatment based on the consequences model is to alleviate symptoms [121; 122; 141].

This original consequences model was tailored to primary-care patients. The changes resulting from this tailoring are shown as dotted lines and *italics* in Figure 6.1. They can be summarized in terms of three adjustments:

1. Adding and starting bottom-up instead of top-down

Our first change was based upon the fact, that, in the original model, beliefs have a central role. However, the focus on thoughts might not fit the more physically orientated way of viewing and communicating of patients [96; 97; 103], and the need to challenge thoughts in cognitive-behavioral therapy has been questioned lately [84].

In our tailored version of the consequences model, we therefore enter the model bottom-up instead of top-down. Herewith, the consequences rather than the beliefs have a central role. By changing and reducing the consequences, beliefs are addressed indirectly, after which the beliefs can be still addressed directly.

2. Aggravating instead of maintaining reactions

Our second change was based upon the fact, that, in the original model, the consequences can maintain UPS. In our view, patients might translate that as personal blame for causing the continuation of their UPS. This does not match primary-care patients' hope of finding clinician's support [98; 104].

In our tailored version of the consequences model, causes are consistently labeled as unknown. The consequences therefore aggravate symptoms rather than maintain UPS. In this way, patients are relieved from blame not only for the cause and existence of UPS, but also for its persistence.

3. Improvement of quality of life instead of symptom alleviation

Our last change was based upon the fact, that, in the original model, the treatment's goal is to alleviate symptoms [121; 122; 141]. However, primary-care patients mainly hope to find clinician's support [98; 104], followed by their goals to improve daily functioning and to cope with UPS [98].

In our tailored version of the consequences model, the treatment's goal is to improve patients' quality of life not only by preventing aggravation of symptoms but also by increasing daily functioning and coping. This expands the opportunities to support patients' reactions and makes support independent of changes in UPS itself, since its causes are explicitly labeled as unknown.

Table 6.1. The cognitive-behavioral techniques used in each session

Session	Training's contents	
	Acquaintance	
1	Plenary define personal goals for the training	
	Plenary present the characteristics of own UPS	
	Consequence of UPS	
2	Physical	Psycho-education on physical arousal
		Stopping physical arousal and replacing it with abdominal breathing and relaxation
	Behavioral	Psycho-education on habits
		Stopping potentially harmful habits and replacing them with incompatible beneficial ones, such as: -drinking warm herbal tea rather than drinking beer to fall asleep in the evening -using skin moisturizer rather than scratching to stop a body itch
3	Behavioral	Psycho-education on under-activity, over-activity, and the combination of both
		Stopping under-activity, over-activity, or the combination from them and replacing them with scheduling various activities at a feasible pace with short breaks
	Physical	Rehearsal: abdominal breathing and relaxation

Table 6.1. The cognitive-behavioral techniques used in each session *(continued)*

Session	Training's contents	
4	Emotional	Psycho-education on the meaning of emotions and on the physical arousal they cause
		Recognizing emotions as an important sign that: -the situation at hand does not correspond with own wishes, needs and expectations -the situation asks for change and improvement
		Stopping physical arousal of emotions and replacing it with abdominal breathing and relaxation
	Various	Rehearsal: abdominal breathing and relaxation, and pacing activities
5	Beliefs	Psycho-education on beliefs
		Stopping dysfunctional beliefs and replacing them with facts and helpful beliefs using Ellis' ABC scheme
	Various	Rehearsal: abdominal breathing and relaxation, and pacing activities
6	Physical	Psycho-education on physical fitness
		Improving physical fitness by doing daily a low-cardiac physical activity, extending it by a minute per day, to a target of 60 minutes twice daily
	Various	Rehearsal: abdominal breathing and relaxation, and pacing activities
7	Cognitive	Psycho-education on information processing
		Stopping dysfunctional information processing and replacing it with a functional information processing
	Social	Summarizing all consequences of own UPS in a scheme and discussing this scheme with an important and trusted person outside the training
	Various	Rehearsal: abdominal breathing and relaxation, pacing activities, and graded exercise
8-12	Various	Stopping dysfunctional problem solving and replacing it with functional problem solving using the five steps of the problem-solving method (1. problem attitude, 2. problem definition, 3. alternative solutions, 4. solution plan, and 5. solution implementation & evaluation)
		Rehearsal: abdominal breathing and relaxation, pacing activities, and graded exercise
	Relapse prevention	
13		Summarizing all discussed techniques
		Assembling the techniques applicable for own UPS in a personal First Aid kit
		Rehearsal: abdominal breathing and relaxation, pacing activities, and graded exercise

Based on this tailored cognitive-behavioral model, a manual was developed for a group training called 'Coping with the consequences of unexplained physical symptoms' [148]. This training consists of 13 weekly two-hour sessions organized in local medical settings. Table 6.1 shows the cognitive-behavioral techniques used in each session.

The control intervention was a waiting list. The waiting period was as long as the period of the intervention; 13 weeks.

Outcomes

To measure improvement in quality of life, we used the *36-item Medical Outcomes Study Short-Form General Health Survey* (SF-36), a validated and reliable self-report questionnaire with 36 questions and fixed-response alternatives for assessing functional health and well-being over the past four weeks [146]. The responses are converted into eight multi-item scales (0-100): Physical functioning, Role functioning physical, Bodily pain, General health, Vitality, Social functioning, Role functioning emotional, and Mental health. These scales can be summarized into the 'Physical component summary', in which the first four of the above eight scales are weighted most heavily; and into the 'Mental component summary', in which the last four of the above eight scales are weighted most heavily [145]. These summaries are transformed into T-scores with a mean of 50 and standard deviation of 10. Higher scores on SF-36 scales indicate a better quality of life.

To measure the intensity of a broad range of psychological problems and psychopathology symptoms, we used the *revised 90-item Symptom Checklist* (SCL-90-R), a validated and reliable self-report questionnaire with 90 questions and fixed response alternatives for assessing the intensity of symptoms over the past week [12]. The responses are summed up in eight multi-item scales: Phobic anxiety, Anxiety, Depression, Somatization, Obsessive-compulsiveness, Interpersonal sensitivity, Hostility, and Sleep difficulties. These scales can be summarized in the 'Global severity index'. Higher scores on SCL-90-R scales indicate a higher number or more severe symptoms.

Primary outcome measures were the 'Physical component summary' and the 'Mental component summary' of the SF-36. Secondary outcome measures were the individual SF-36 scales and the SCL-90-R scales.

For the SF-36, the manual provides an algorithm to compute the scale scores with a single norm for the maximum tolerated percentage of missing items. In this algorithm, the score of a SF-36-scale is only computed, if a patient has completed at least 50% of the items belonging to this SF-36 scale. If this is the case, the patient's available items belonging to the same scale are added up and the resulting sum is divided by the number of available scale items of the same patient. If the number of missing items on a SF-36 scale exceeds the 50% percentages, the score for this scale remains missing.

For the SCL-90-R, the manual provides an algorithm to compute the scales scores with norms for the maximum tolerated number of missing items. For the scale 'Sleep difficulties', the maximum tolerated number of missing items is one; for the other scales, this maximum is two. By this, the maximum tolerated percentage of missing items of the scales ranges from 67 to 98%. We chose to set the maximum tolerated percentage of missing items for all scales at 75%. In the resulting algorithm, the score of a SCL-90-R scale is only then computed, if a patient has completed at least 75% of the items belonging to this SCL-90-R scale. If this is the case, the patient's available items belonging to the

same SCL-90-R scale are added up and the resulting sum is divided by the number of available scale items of the same patient. If the number of missing items on a SCL-90-R scale exceeds this 75% percentage, the score for this scale remains missing.

Sample size

The sample size required was calculated by power analysis. For power analysis, we applied SPSS version 17 and the mixed-model ANOVA procedure described by Aberson [2]. The repeated-measurement correlation required for the power analysis was estimated on basis of the SF-36 manual [145]. In the manual, a two-week test-retest correlation of 0.80 was reported for the SF-36 summary scale 'Mental component summary' and 0.89 for the 'Physical component summary'. Taking into account that a reduction of these correlations should be expected as the time period between the two measurements in our study was longer and included the intervention, the correlation was estimated at 0.75. The effect size for the power analysis was estimated at 0.40 based on a review [96], in which the effect sizes for cognitive-behavioral treatments in UPS compared with control conditions centered around 0.40. These values for correlation and effect size, in combination with an alpha of 0.05 and a beta of 0.20 led to a required sample size of 51 in each group. Adjusted for a dropout of one third, this resulted in a total sample size of 153. The presented procedure to estimate the required sample size deviates from the one described in the original trial protocol [149], as the original power analysis did not match the intended and original statistical analysis plan.

Randomization—Sequence generation

Patients were assigned either to the training or to the waiting list according to a computer generated randomization list. This randomization list was generated just before the start of the next training for enrolled patients who had completed all baseline measurements. As each training was followed by the next one in quick succession and holidays accounted for the only gaps between one training and another, a randomization list was usually generated every other 13 weeks.

Randomization—Allocation concealment

As the randomization list was generated after the patients were assessed for eligibility and enrolled, allocation was certainly concealed for patients and assessors.

Randomization—Implementation

The randomization list was generated by an investigator who had no clinical involvement in the trial, and who was working in a different building than the buildings where assessment and enrollment were done.

Patients were assessed and enrolled by seven psychologists who had been trained in the SCID-I/P over several sessions. These psychologists were not involved in other parts of the study or patients' treatment.

Patients were assigned after enrollment according to the randomization list by a psychologist who was not involved in the generation of the randomization list, nor in the assessment and enrollment of patients. Patients were informed about their assignments by a letter posted to their home address.

Blinding

Patients and trainers could not be blinded for the group assignment, as the control condition was a simple waiting list. The data were imported and analyzed after patients had completed the trial.

Statistical methods

Effectiveness of the group training

In the randomized controlled trial, the comparability of the patients' baseline-variables between patients who completed the randomized controlled trial and those who dropped out was analyzed with the two-tailed t-tests for independent samples for the continuous variables, with the two-tailed Mann-Whitney U-tests for the ordinal variables and with the chi-square tests for the categorical variables. The effects of the training were analyzed with linear mixed modeling.

Preservation of the effect of the group training

In the non-randomized, observational follow-up, the comparability of the patients' baseline-variables between patients who could be followed up and those who were lost was analyzed with the two-tailed t-tests for independent samples for the continuous variables, with the two-tailed Mann-Whitney U-tests for the ordinal variables and with the chi-square tests for the categorical variables. The preservation of the effects of the training was analyzed with linear mixed modeling.

Significance level

All statistical analyses were done with the significance level fixed at 0.05 (two-tailed).

Results

Participant flow

Figure 6.2 shows the flow of patients through the study.

Recruitment

Patients were recruited between February 2005 and September 2008 in general practices, in outpatient clinics at general hospitals, and by our secondary community mental health service in and around Rotterdam, the Netherlands. The follow-up ended in December 2009; one year after the intervention group of the last randomization had completed the training.

Baseline data

Table 6.2 and Table 6.3 list the characteristics of the 162 randomized patients, 133 of whom (82%) provided outcome data. There were no significant differences between the 133 patients with primary endpoint outcome data and the 29 who dropped out the randomized controlled trial with regard to the following: UPS characteristics, the number of co-morbid DSM-IV Axis I and Axis II classifications, referrer characteristics, sociodemographic characteristics, and outcome variables.

Intervention data

In total, the training was conducted 20 times in four different local medical settings, with between five and nine patients per intervention (an average of six patients per intervention). The mean number of attended sessions by the patients who were randomly assigned to the training and provided outcome data was eleven. The minimum number of attended sessions was six.

Each of the 20 groups was led by one of six psychologists with a Master's degree, four of whom had had at least three years' post-Master's experience with group therapy and/or cognitive-behavioral therapy. To compensate for the lack of experience of the other two psychologists, they observed the developer of the manual (LZ) during a group session before jointly leading another group in their own session on the following day. (They led only one 13-week training.) To increase treatment integrity and positive group dynamics, all psychologists familiarized themselves with the tailored consequences model and the manual's line of reasoning by going through the manual before each session under the supervision of LZ.

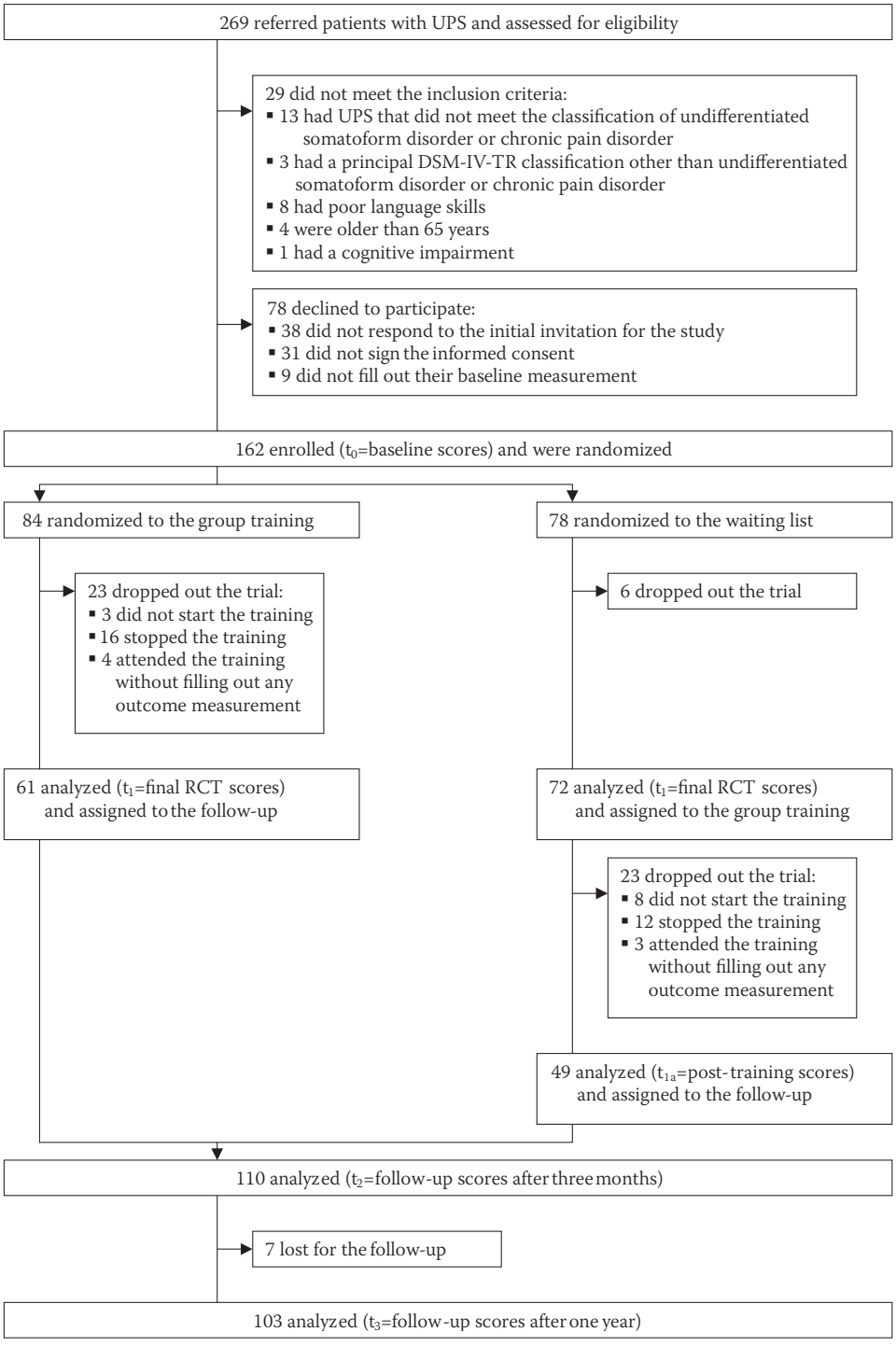


Figure 6.2. Patient flow

Table 6.2. Patients' clinical characteristics

Clinical characteristic	Group training (n=84)	Waiting list (n=78)
Duration of UPS in years		
median	8	9.5
interquartile range	3-16	3-17
Classification of UPS by SCID-I/P		
undifferentiated somatoform disorder	32	31
chronic pain disorder	52	47
Presence of one or more comorbid DSM-IV Axis I disorders	38	29
Classification of comorbid DSM-IV Axis I disorders		
mood disorder (lifetime)	13 (40)	11 (30)
anxiety disorder (lifetime)	20 (36)	27 (41)
substance-related disorder (lifetime)	1 (12)	0 (6)
eating disorder (lifetime)	1 (4)	0 (2)
psychotic disorder (lifetime)	0 (0)	0 (1)
somatization disorder	14	10
hypochondriasis	1	1
adjustment disorder	2	2
Presence of one or more comorbid DSM-IV Axis II disorders	25	22
Classification of comorbid DSM-IV Axis II disorders		
paranoid personality disorder	6	12
schizoid personality disorder	2	3
schizotypal personality disorder	1	1
anti-social personality disorder	0	1
borderline personality disorder	2	5
histrionic personality disorder	1	1
narcissistic personality disorder	0	2
avoidant personality disorder	15	14
dependent personality disorder	2	2
obsessive compulsive personality disorder	14	10
Referrer		
primary medical service	41	41
secondary medical service	28	23
secondary mental service	15	14

Numbers analyzed

The statistical analyses were conducted according to the intention-to-treat principle [88], as the data of all patients who were randomized were included in the linear mixed modeling.

Table 6.3. Patients' sociodemographic characteristics

Sociodemographic characteristic	Group training (n=84)	Waiting list (n=78)
Gender		
female	67	64
male	17	14
Age in years		
mean	46	44
interquartile range	38-53	35-52
Nationality		
Dutch	72	69
other	12	9
Marital status		
married or living with partner	62	48
unmarried, divorced or widowed	22	30
Highest education completed		
primary school or less	7	7
lower vocational or general secondary education	29	25
intermediate vocational or higher general secondary education	33	24
higher vocational, pre-university or university education	15	21
missing	0	1
Employment		
employed	29	28
unemployed	55	50

Outcomes and estimation

Effectiveness of the group training

Table 6.4 shows the estimates for the effect of the training on the primary and secondary endpoints of the randomized controlled trial. The training had a significant effect on the primary outcome measure 'Physical component summary' (p=0.002). The effect size was medium (Cohen's d=0.38) according to Cohen's statistical guidelines [31]. No effect of the training was found for the primary outcome measure 'Mental component summary'. On the secondary outcome measures of the SF-36, scales in favor of the training indicating significantly better functioning were: Role functioning physical (Cohen's d=0.43; p=0.01), Bodily pain (Cohen's d=0.51; p=<0.001), Vitality (Cohen's d=0.30; p=0.05), Social functioning (Cohen's d=0.36; p=0.01), and Role functioning emotional (Cohen's d=0.44; p=0.01). On the secondary outcome measures of the SCL-90-R, scales in favor of the training indicating a lower number or less severe symptoms were: Somatization (Cohen's d=-0.23; p=0.05) and Sleep difficulties (Cohen's d=-0.25; p=0.04).

Table 6.4. Estimates for training and waiting group

Scale	Intercept Estimate [95% CI]	Time Estimate [95% CI]	Time * Training Estimate [95% CI]	Training vs. Waiting groep	
				Cohen's d	p
Primary endpoint					
SF-36 scale					
physical component summary	31.2 [30.1 - 32.8]	1.5 [0.04 - 3.0]	3.4 [1.3 - 5.5]	0.38	0.002
mental component summary	45.2 [43.5 - 46.7]				
Secondary endpoint					
SF-36 scale					
physical functioning	50.9 [47.1 - 54.6]	2.2 [-1.3 - 5.6]	4.7 [-0.3 - 9.7]	0.19	0.06
role functioning physical	15.6 [11.4 - 19.8]	5.9 [-0.3 - 12.1]	11.7 [2.6 - 20.7]	0.43	0.01
bodily pain	33.2 [30.3 - 36.2]	0.3 [-3.4 - 3.9]	9.9 [4.8 - 15.1]	0.51	<0.001
general health	38.0 [35.2 - 40.7]	3.8 [1.3 - 6.4]			
vitality	33.4 [3.1 - 36.2]	3.4 [-0.4 - 7.3]	5.4 [0.1 - 10.7]	0.30	0.05
social functioning	49.2 [45.4 - 52.9]	1.6 [-3.3 - 6.6]	8.6 [1.7 - 15.5]	0.36	0.01
role functioning emotional	72.1 [62.7 - 81.5]	-10.1 [-20.3 - 0.1]	18.4 [3.4 - 33.3]	0.44	0.01
(training group baseline)[1)]	-13.4 [-26.5 - -0.4]				
mental health	62.0 [60.1 - 65.9]				
SCL-90-R scale					
phobic anxiety	9.2 [8.6 - 9.8]				
anxiety	17.6 [16.5 - 18.7]				
depression	31.7 [30.0 - 33.5]	-1.9 [-3.4 - -0.5]			
somatization	29.2 [27.8 - 30.5]	-2.0 [-2.6 - 0.2]	-2.0 [-4.0 - 0.0]	-0.23	0.05
obsessive-compulsive	20.7 [19.7 - 21.7]	-1.2 [-2.1 - -0.4]			
interpersonal sensitivity	26.7 [25.2 - 28.2]				
hostility	8.5 [8.0 - 9.0]				
sleep difficulties	8.0 [7.5 - 8.6]	-0.4 [-1.0 - 0.2]	-0.9 [-1.8 - 0.0]	-0.25	0.04
global severity index	165.5 [158.0 - 173.0]	-8.1 [-13.3 - -2.8]			

Note: Insignificant effects are not presented in this table.
[1)] Role functioning at baseline was different between the training group and the waiting group.

Preservation of the effect of the group training

Table 6.5 shows the estimates for the effects of time on the primary and secondary endpoints of the non-randomized, observational follow-up. At each time point, time did not eliminate the effects of the training. In contrary, for the primary outcome measure 'Physical component summary', the effect increased from Cohen's d 0.39 to 0.49 at three-months follow-up and Cohen's d was still 0.49 at one-year follow-up. A similar trend was observed for the secondary outcome measures 'Physical functioning' and 'Obsessive-compulsive'.

Table 6.5. Estimates at each time point

Scale	Model estimates				Post training		Three-months follow-up		One-year follow-up	
	Intercept [95% CI]	Time [95% CI]	Time² [95% CI]	Log-time [95% CI]	Estimate [95% CI]	d[1)]	Estimate [95% CI]	d[1)]	Estimate [95% CI]	d[1)]
Primary endpoint										
SF-36 scale										
physical component summary	31.4 [30.0 - 32.9]	-0.3 [-0.5 - -0.1]		3.3 [2.2 - 4.4]	3.6 [2.6 - 4.6]	0.39	4.5 [3.4 - 5.7]	0.49	4.5 [3.2 - 5.7]	0.49
mental component summary	44.9 [43.1 - 46.6]	-0.3 [-0.7 - 0.0]		2.2 [0.5 - 3.9]	2.0 [0.5 - 3.5]	0.18	2.2 [0.5 - 3.9]	0.20	0.9 [-1.0 - 2.8]	0.08
Secondary endpoint										
SF-36 scale										
physical functioning	51.5 [47.7 - 55.3]			2.2 [1.1 - 3.3]	3.1 [1.5 - 4.6]	0.12	4.3 [2.1 - 6.5]	0.17	6.1 [3.0 - 9.2]	0.25
role functioning physical	15.7 [10.7 - 20.7]	-1.5 [-2.5 - -0.5]		13.9 [8.8 - 18.9]	14.8 [10.1 - 19.4]	0.45	18.1 [12.7 - 23.4]	0.56	16.1 [9.2 - 23.1]	0.50
bodily pain	33.2 [30.2 - 36.3]	-5.5 [-10.0 - -1.1]	0.2 [0.0 - 0.4]	17.0 [0.0 - 27.1]	8.8 [5.8 - 11.8]	0.45	7.0 [3.9 - 10.2]	0.36	8.4 [4.1 - 12.8]	0.43
general health	37.9 [35.1 - 40.8]	-0.6 [-1.0 - -0.1]		5.5 [30.0 - 80.1]	6.0 [3.7 - 8.3]	0.33	7.4 [4.8 - 10.0]	0.40	7.0 [4.1 - 9.9]	0.38
vitality	33.4 [30.5 - 36.3]	3.0 [2.1 - 3.9]	-0.2 [-0.2 - -0.1]		7.6 [5.4 - 9.7]	0.39	12.2 [8.8 - 15.5]	0.63	8.6 [5.2 - 12.0]	0.45
social functioning	49.2 [45.4 - 53.1]	-0.9 [-1.7 - -0.2]	8.2 [4.2 - 12.3]		8.7 [5.0 - 12.3]	0.35	10.5 [6.4 - 14.6]	0.42	9.1 [4.5 - 13.6]	0.36
role functioning emotional	65.6 [60.3 - 70.8]									
mental health	62.6 [59.7 - 65.6]	1.1 [0.4 - 1.8]	-0.1 [-0.1 - 0.0]		2.7 [0.9 - 4.5]	0.14	4.2 [1.4 - 7.1]	0.22	1.6 [-1.8 - 5.1]	0.09
SCL-90-R scale										
phobic anxiety	9.3 [8.6 - 9.9]	0.1 [0.0 - 0.2]		-0.5 [-0.9 - -0.1]	-0.4 [-0.8 - 0.0]	-0.10	-0.4 [-0.9 - 0.0]	-0.10	0.0 [-0.6 - 0.6]	0.00
anxiety	17.9 [16.8 - 19.1]	-0.4 [-0.6 - -0.2]	0.02 [0.01 - 0.03]		-0.9 [-1.5 - -0.4]	-0.12	-1.5 [-2.3 - -0.6]	-0.20	-0.9 [-2.1 - 0.2]	-0.12
depression	31.8 [30.0 - 33.5]	0.4 [0.1 - 0.6]		-3.1 [-4.4 - -1.9]	-3.2 [-4.3 - -2.0]	-0.28	-3.7 [-5.1 - -2.3]	-0.33	-2.8 [-4.7 - -0.8]	-0.24
somatization	29.2 [27.9 - 30.4]	0.4 [0.2 - 0.6]		-3.0 [-4.0 - -2.1]	-3.1 [-4.0 - -2.2]	-0.38	-3.8 [-4.8 - -2.7]	-0.45	-3.0 [-4.5 - -1.6]	-0.36
obsessive-compulsive	20.7 [19.7 - 21.7]	-0.5 [-0.7 - -0.3]	0.02 [0.01 - 0.04]		-1.3 [-1.8 - -0.8]	-0.20	-2.2 [-3.0 - -1.4]	-0.34	-2.2 [-3.3 - -1.1]	-0.34
interpersonal sensitivity	26.7 [5.1 - 28.2]									
hostility	8.3 [7.8 - 8.8]									
sleep difficulties	8.0 [7.5 - 8.6]	0.1 [0.03 - 0.2]		-0.9 [-1.4 - -0.4]	-0.9 [-1.3 - -0.5]	-0.25	-1.0 [-1.5 - -0.5]	-0.29	-0.7 [-1.3 - -0.1]	-0.19
global severity index	165.5 [158 - 173]	1.4 [0.5 - 2.3]		-11.1 [-15.6 - -6.6]	-11.3 [-15.4 -7.1]	-0.23	-13.4 [-18.5 - -8.3]	-0.27	-10.1 [-17.9 - -2.5]	-0.21

Note: Insignificant effects are not presented in this table. [1)] d = Cohen's d compared with baseline.

Ancillary analyses

To explore whether patients who had one-year follow-up scores differed from patients who had no one-year follow-up scores, these two groups were compared with each other with regard to the following: UPS characteristics, the number of co-morbid DSM-IV Axis I classifications, referrer characteristics, sociodemographic characteristics, and outcome variables. Patients with one-year follow-up scores were significantly older (mean=46.69; SD=10.79) and reported significantly more vitality (mean=35.58; SD=17.56), and significantly less hostility (mean=7.99; SD=2.68) than patients without one-year follow-up scores (age: mean=42.44; SD=11.09; p=0.02; SF-36 scale 'Vitality': mean=29.60; SD=17.88; p=0.04, and SCL-90-R scale 'Hostility': mean=9.53; SD=4.78; p=0.03).

Adverse events

One adverse event was reported in this study. After the training, one patient reported rumination about possible death of beloved people, which tired her out. For this patient, psychotherapy was arranged, in which she engaged. Further details of this patient are described in Chapter 4 of this thesis and have been published elsewhere [172].

Discussion

Interpretation

The effect of a cognitive-behavioral group training on the quality of life was studied in patients with UPS. The group training was based on the consequences model tailored to primary-care patients with UPS and provided by a secondary community mental health service reaching out into the primary care. The group training was effective in improving the physical domain of quality of life, which was the domain patients reported as most burdensome at baseline. This positive effect was preserved during the entire one-year follow-up period. These results are remarkable, as studies have shown that the prognosis of UPS becomes more unfavorable if the duration of UPS is longer [63; 74; 75; 124], or if UPS is classified as a somatoform disorder [10; 63]. In our study group, the median of the duration of UPS was nine years, and UPS had been classified as undifferentiated somatoform disorder or as chronic pain disorder.

Considering these effects, further research on this training seems to be worthwhile. The effects might differ between various subgroups within patients with UPS. Further research could explore, whether some subgroups benefit more than others. If the latter is the case, allocation and selection might improve effectiveness even more. Also, it would be interesting to explore whether the training also reduces costs by reducing medical utilization, and productivity losses due to UPS. This would make the training not only more interesting from patients' but also from societal perspective.

Generalizability

Various terms are used for unexplained physical symptoms. Examples of other terms used for these symptoms are Medically Unexplained Physical Symptoms (MUPS), Functional Somatic Symptoms (FSS), abridged somatization, and multisomatoform disorder [43; 47; 77]. The use of different terms and different definitions makes the communication about these symptoms between clinicians and researchers within and between disciplines difficult and reduces generalizability. This might be resolved in the next revision of the American Psychiatric Association's Diagnostic and Statistical Manual for Mental Disorders (DSM). Currently, the proposed revision is to name these symptoms as Somatic Symptom Disorder, which is defined as persistent distressing somatic symptoms in combination with excessive thoughts, feelings, and behaviors in response to these somatic symptoms [7]. Pending this revision, we chose among all frequently used terms the term Unexplained Physical Symptoms (UPS), because this term reflects best that physical, psychological and social causes and effects are not or not easily separated from each other, and are mostly interrelated without a clear starting or finishing point. By using the term UPS, we acknowledged these interrelationships, promoted transparency in the communication to all stakeholders; patients, clinicians and researchers, and followed the recommendation for terminology on these symptoms, which includes "to remove language that is potentially pejorative to patients" [77].

The prevalence of having one or more co-morbid DSM-IV Axis I disorders in our study was 41%. The three most commonly comorbid DSM-IV Axis I disorders were anxiety (29%), mood (15%), and somatization (15%) disorder. These prevalences are comparable with earlier findings in patients with UPS. In this patient group, studies found prevalences of comorbid anxiety and/or depressive disorders in primary care ranging from 26 [34] to 54% [86]. The prevalence of a comorbid anxiety disorder was 17% and the prevalence of a comorbid depressive disorder was also 17% [34]. It is known [59], that patients with UPS have a higher rate of current mood disorder or current anxiety disorder than either healthy controls or patients with phenomenologically similar medical diseases of known organic pathology. Including patients with co-morbid DSM-IV Axis I disorders makes our results generalizable to a wider group of patients with UPS than usually selected for scientific trials, and more similar to the patient group seen in routine clinical practice.

The prevalence of having one or more personality disorders in our study was 29%. The three most commonly personality disorders were avoidant (17.9%), obsessive compulsive (14.8%), and paranoid (11.1%) personality disorder. These prevalences are in line with earlier findings in this group of patients. Studies found prevalences of personality disorders in patients with UPS ranging from 0 to 88.6% [33; 49; 50; 58; 67; 83; 87; 99; 110; 135]. In these studies, the most commonly personality disorder for patients with UPS differed between obsessive compulsive [33; 58; 87; 99; 135], histrionic [50; 67], avoidant [99; 110], dependent [18; 87] and paranoid [49] personality disorder.

Our findings on the prevalence of personality disorders were quite similar to the rates reported in the study on patients with chest pain measuring personality disorders using a self-report questionnaire [33]. This study reported a prevalence of 39%, in which the three most commonly reported personality disorders were obsessive-compulsive (23.3%), avoidant (13.8%), and paranoid (13.2%) personality disorder [33]. Differences in prevalences of personality disorders between studies might be explained by the use of different instruments for the assessment of personality disorders, but also by the use of different definitions for unexplained physical symptoms (e.g. somatizing patients and somatization disorder). As our definition of unexplained physical symptoms was symptoms fulfilling the DSM-IV criteria for an undifferentiated somatoform disorder or a chronic pain disorder, prevalences in our study might also be slightly lower than in somatoform disorders in general, because studies [50; 99] suggested that both undifferentiated somatoform disorder and chronic pain disorder were less frequently associated with personality pathology than the other somatoform disorders. Due to the use of validated instruments for both the classification of UPS and personality disorders and the comparability of our findings with earlier findings, we believe our results to be reliable and generalizable.

The training is theory-based and elaborately described in the manual [148]. It was conducted by six different psychologists with different experience levels at four different local medical settings. This suggests that the training is transferable to different circumstances.

Conducting the training belonged to the daily activities of the psychologists and was financed within the current reimbursement practice. By this, the training could be implemented without research funds. Kathol et al. [66] showed the relevance for this kind for generalizability, as most evidence-based programs integrating mental health services in primary care could not be successfully implemented after completion of the study due to the fact that research funds were not substituted within the current reimbursement practice.

Limitations

The options for the study were limited by the fact that it was part of daily activities of a secondary community mental health service. Because patients on the waiting list had to wait only 13 weeks for the group training – the same period as the training itself – the study was deprived of a control condition for the three-month and one-year follow-ups. However, our time frame of follow-up assessments was longer than the usual time frame of intervention studies for UPS that ranged from three to 12 months with a mean of six months [4].

Not only the duration of the waiting list for controlling the influence of time and other not-intervention-related circumstances, but also the lack of a control condition for

the influence of intervention-related aspects was a limitation. Because of this limitation, the measured effects could not be attributed to the specific therapeutic interventions of our training. If a control intervention group (e.g. relaxation, solely psycho-education, self help, individual treatment) had been included, it would have been possible to explore whether the training itself had supplementary effects in comparison to other interventions or individual treatment.

Another limitation of our study is, that the inter-rater-reliability was not calculated for the *Structured Clinical Interview for DSM-IV Axis I Disorders/Patient edition* (SCID-I/P), which verified whether patients fulfilled the inclusion criteria for undifferentiated somatoform disorder or chronic pain disorder. This is especially regrettable, as the number of UPS classified as undifferentiated somatoform disorder was lower than the number of UPS classified as chronic pain disorder – the opposite of what was found in a study in Dutch general practices [34]. To clarify this difference, we examined the SCID-I/P interviews more closely. This showed that, due to the interviewers' or patients' emphasis on pain in the presence of a broad spectrum of symptoms, syndromes such as fibromyalgia or chronic fatigue syndrome had sometimes been misclassified as chronic pain disorder. These misclassifications might have inflated the number of chronic pain disorders at the expense of undifferentiated somatoform disorder.

Not only the comparability of interviews, but also the comparability of the training's sessions in different groups was not measured. As supervision was given by the developer of the manual (LZ) before each session, treatment integrity and comparability were stimulated but they were not verified. If the group sessions had been recorded, they could have been rated by independent raters and treatment integrity could have been verified.

Randomization was used to reach comparability between the patients in the group training and the patients on the waiting list. Notably, this randomization resulted in an imbalance of distribution of living with or without a partner over the training and the waiting group, although this imbalance was not significant (p=0.13). Nevertheless, such imbalance might have influenced the results in favor of the training, as this sociodemographic variable could be seen as an indicator of social support and the ability to have stable relationships.

Overall evidence

Earlier studies have found that cognitive-behavioral therapy improved physical symptoms, psychological distress, and functional status [96; 130]. The effect sizes for this therapy compared with control conditions centered around 0.40 [96]. Physical symptoms appeared to be the most responsive [96; 130], although in some studies for specific syndromes, such as chronic fatigue syndrome and fibromyalgia, the opposite was found, and the effect size for psychological distress was larger [96]. Improvement of the physical symptoms could occur whether or not psychological distress was decreased

[78]. Preservation of the positive effects was observed in 6-months to one-year follow-up assessments [96].

Our findings seemed to be consistent with these earlier studies as they showed a similar improvement of functional status and symptoms, more responsiveness of physical symptoms in comparison to psychological symptoms, and the preservation of these effects over the one-year follow-up period. The effect size of 0.38 in the randomized controlled trial and the effect size of 0.49 in the non-randomized one-year follow-up might even be considered to be relatively high, because our training was designed to be easily accessible, and, thereby, might have included more patients with higher resistance to psychological interventions.

For this, the tailoring of the consequences model for primary-care patients might have been essential. It was only after doing so that we discovered that, due to low acceptance [11], and no effectiveness [8], two previous attempts to use the original consequences model in primary care had failed. Although most patients in our study had been referred by medical services, especially by general practitioners, 'only' 78 of the 269 (29%) patients did not attend their first appointments (so-called 'no shows'); this no-show figure was substantially lower than the estimated 50 to 80% of patients who refuse to be referred to mental health services [5]. Patients also seemed to accept the training itself: 65 of the 84 who were randomized to it (77%), and 52 of the 72 who waited for it (72%) really attended the training.

By seeking close collaboration with medical centers and by offering treatment at these centers, we might not only have broadened the accessibility of mental health services for primary-care patients. As physicians rated the problems of getting mental health services for their patients twice as high as the problems of getting other specialty services [32], we might also have simplified the access of mental health services for physicians.

The success rate of referrals from medical care services to the training might still be improvable. The three most common reasons for failure to seek treatment after referral are 1.) the problem has resolved, 2.) patients need to wait before treatment starts, and 3.) a lack of motivation [103]. With regard to the first reason, it is suggested by the long duration of UPS in our patients, and also by the overall low recovery rate in patients with somatoform disorders [10], that the problem had not resolved. But the second reason – having to wait for treatment – was certainly an issue: those who had to wait, such as those on the waiting list, complained about it. Indeed, some could not bring themselves to wait and left the trial. Therefore, if this training is implemented in routine clinical practice, a short waiting period before treatment starts is advisable. The third reason – lack of motivation to actualize the referral – revealed another area in which there is scope for further improvement. Patients commented that their physicians had suggested that their complaints were 'all in their mind'. In certain cases, the sense of not being taken seriously made them delay seeking treatment and made them express anger about

it at their first appointment. Feeling disrespected is a factor that is known to influence unnotified no-shows [80].

Perhaps the number of successful referrals might be increased if physicians are trained to use the language of the tailored consequences model to explain the goals of the referral and the treatment – without having to do the cognitive-behavioral interventions themselves. Asking them to do these interventions themselves might not be as effective because of the implementation issues mentioned in the introduction, but also because of difference in the education between physicians and psychologists, and the low volume of doing psychological treatment for general practitioners in comparison to psychologists. In medicine, it is a well-established fact, that outcome raises with higher volumes [56].

In short, the cognitive-behavioral group training tailored to patients with UPS in primary care and provided by an outreaching secondary mental health service appears to be effective and to broaden the accessibility of the treatment of UPS.

Chapter 7

Predicting the outcome of a cognitive-behavioral group training for patients with unexplained physical symptoms: a one-year follow-up study

Abstract

Background

Although Cognitive-Behavioral Therapy (CBT) is effective for Unexplained Physical Symptoms (UPS), some therapists in clinical practice seem to believe that CBT outcome will diminish if psychiatric comorbidity is present. The result is that patients with a psychiatric comorbidity are redirected from treatment for UPS into treatment for mental health problems. To explore whether this selection and allocation are appropriate, we explored whether CBT outcomes in UPS could be predicted by variables assessed at baseline and used in routine-practice assessments.

Methods

Patients (n=162) with UPS classified as undifferentiated somatoform disorder or chronic pain disorder were followed up until one year after they had attended a CBT group training. The time-points of the follow-up were at the end of CBT (immediate outcome), three months after CBT (short-term outcome), and one year after CBT (long-term outcome).

CBT outcome was measured using the 'Physical component summary' of the SF-36, which was the primary outcome measure in the randomized controlled trial that studied effectiveness of the CBT group training. Predictors were: 1.) psychological symptoms ('Global severity index' of SCL-90-R), 2.) personality-disorder characteristics (sum of DSM-IV Axis II criteria confirmed), 3.) psychiatric history (past presence of DSM-IV Axis I disorders), and 4.) health-related quality of life in the mental domain ('Mental component summary' of SF-36). The effect of this predictor set was explored using hierarchical multiple regression analyses into which these predictors had been entered simultaneously, after control for: a.) pretreatment primary outcome scores, b.) age, c.) gender, d.) marital status, and e.) employment.

Results

The predictor set was significant only for short-term CBT outcome, where it explained 15% of the variance. A better outcome was predicted by more psychological symptoms, fewer personality-disorder characteristics, the presence of a psychiatric history, and a better quality of life in the mental domain.

Conclusions

As the predictors do not seem to predict CBT outcome consistently over time, the need for selection and allocation of patients with UPS for CBT is doubtful. It seems that this would unnecessarily deprive patients of effective treatment.

Background

Although Cognitive-Behavioral Therapy (CBT) is effective for Unexplained Physical Symptoms (UPS) [5; 6; 48; 86; 111; 152], some therapists in clinical practice seem to believe that it is not equally effective for all patients with UPS. Instead, they assume that outcome will be poorer in patients whose quality of life may have been affected by a psychiatric comorbidity such as depression, anxiety disorder, personality-disorder, or their psychiatric history.

Inconsistent findings have been produced by studies that investigated whether such comorbidity did indeed predict poor outcome [16; 19; 20; 33; 39; 60; 69; 77; 95; 96; 101; 107; 121; 125; 132]. Some studies showed that poor treatment outcome for UPS was predicted by concurrent depressive symptoms [125], anxiety symptoms [33], personality-disorder characteristics [77], a psychiatric history [16; 20] or poor health-related quality of life [16]. Other studies used the same predictors to conclude differently. Thus, for concurrent depressive symptoms, one study found that depressive symptoms predicted a better outcome [132], while others showed no influence [19; 33; 39; 60; 69; 77; 95; 96; 101; 107; 121]. For concurrent anxiety symptoms, another study found that anxiety, too, predicted a better outcome [107], while others showed no influence [19; 39; 60; 69; 77; 95; 96; 121]. For concurrent personality disorders, two further studies found that a personality disorder did not predict outcome – though they also implied that a personality disorder might increase the drop-out rate [95; 96]. For psychiatric history, a further study showed no influence on outcome [125]. For health-related quality of life, another study reported that poorer functioning valued by assessors and a poorer quality of life reported by patients were associated with better outcome [19]. Conclusions on whether psychiatric comorbidity predicted outcome differed not only between studies, but also within them [16; 19]. For example, one study [16] found that depressive symptoms did not predict post-treatment outcome, but did predict better three-months follow-up outcome.

One possible reason for these inconsistent findings on predicting CBT outcome in UPS is that the impact of psychiatric comorbidity was blurred by differences in the outcome scores at baseline or in sociodemographic variables at baseline. Various studies showed that the outcome was influenced by the pretreatment score on the outcome measure [16; 19; 33], and by sociodemographic variables such as age [16; 33; 101; 107], gender [19], marital status [132], or having paid work [19; 69].

To find predictors that consistently predict CBT outcome over time, we explored whether psychological symptoms, personality-disorder characteristics, psychiatric history, and health-related quality of life in the mental domain assessed at baseline predicted CBT outcome on the primary outcome measure at the end of CBT (immediate outcome), three months after CBT (short-term outcome), and one year after CBT (long-term outcome), after control for pretreatment scores on the outcome measure and for

sociodemographic variables. In line with clinical practice, that was supported but also contradicted by a number of studies, we hypothesized that better CBT outcome would be predicted by the following: fewer psychological symptoms and personality-disorder characteristics, the absence of a psychiatric history, and a better quality of life in the mental domain.

Methods

Design

The data for this study were collected in a randomized controlled trial on the effectiveness of cognitive-behavioral group training (CBT) for patients with UPS [175]. Patients with UPS were randomized either to CBT or to a waiting list after they had completed the baseline measurement (T_0). The second measurement (T_1) was made directly after the training (13 weeks), or, for those on the waiting list, after the same period. The preservation of the effect of the group training was investigated in a non-randomized one-year follow-up. To this end, patients who had been randomized to the waiting list and had waited started the training after their second measurement (T_1). Patients who had attended the training were followed-up three months after the end of treatment (T_2), and again one year later (T_3).

The study was approved by the Erasmus Medical Research Ethics Committee, and registered in the Dutch Trial Register (NTR 1609) [171]. A detailed description of the study protocol can be found in Chapter 3 and has been published elsewhere [173].

Participants

Patients were recruited between February 2005 and September 2008 in general practices, in outpatient clinics at general hospitals, and by Riagg Rijnmond, a secondary community mental health service for the greater Rotterdam area in the Netherlands. General practitioners and specialists were asked to refer patients aged between 18 and 65 years whose physical symptoms, according to their clinical judgment, could not be fully explained on the basis of a known medical condition. Patients were included if they signed the informed consent and if their UPS fulfilled the DSM-IV criteria for an undifferentiated somatoform disorder or a chronic pain disorder.

We chose UPS classified with DSM-IV as 'undifferentiated somatoform disorder' or as 'chronic pain disorder', as these disorders were given clinical relevance by their high prevalence – in general practices, they are the most prevalent of all somatoform disorders [38] – and as they could be selected by valid and reliable instruments. Undifferentiated somatoform disorder and chronic pain disorder are non-overlapping disorders because of criterion E in the DSM-IV criteria for 'undifferentiated somatoform

disorder', which states that the 'undifferentiated somatoform disorder' can be assigned only if the symptoms are not better accounted for by another mental disorder such as another somatoform disorder.

To verify whether UPS fulfilled all DSM-IV criteria for either 'undifferentiated somatoform disorder' or 'chronic pain disorder', we used the *Structured Clinical Interview for DSM-IV Axis I Disorders/Patient edition* (SCID-I/P) [55], a semi-structured validated and reliable interview for making the major DSM-IV Axis I diagnoses.

Patients were excluded if they did not provide informed consent, or if poor language skills or handicaps such as cognitive impairment prevented them from understanding the CBT group training.

CBT group training

The intervention, a CBT group training called 'Coping with the consequences of unexplained physical symptoms', is a weekly two-hour manual-based [170] training that is held over a 13-week period. It uses the following CBT techniques: psycho-education, response prevention, pacing activity, graded activity, graded exercise, problem-solving, breathing and relaxation exercise, cognitive intervention using the Ellis' ABC worksheet, and relapse prevention. Its aim is to improve health-related quality of life. A more detailed description of this CBT can be found in Chapter 3-5 and has been published elsewhere [172; 173; 174].

CBT outcome measurement

In the randomized controlled trial, the primary outcomes were the summary scales of the *36-item Medical Outcomes Study Short-Form General Health Survey* (SF-36) [168]: Physical Component Summary' (PCS) and 'Mental Component Summary' (MCS). In the present study, the PCS was chosen as outcome measurement, because patients reported the quality of life in the physical domain as most burdensome. The group training significantly improved quality of life in the physical domain, and this positive effect was maintained during the entire one-year follow-up period [175].

The PCS summarizes functional health and well-being in the physical domain over the past four weeks. This summary is transformed into T-scores with a mean of 50 and standard deviation of 10. A higher summary score indicates a better quality of life.

The CBT outcome score was defined as the difference between the baseline PCS score and the following: post-treatment PCS scores (immediate outcome); three-month follow-up PCS scores (short-term outcome); and one-year follow-up PCS scores (long-term outcome). A higher CBT outcome score indicates more improvement of quality of life in the physical domain.

Predictors

Psychological symptoms

Psychological symptoms were measured using the *revised 90-item Symptom Checklist* (SCL-90-R). This is a validated and reliable self-report questionnaire with 90 questions and five fixed-response alternatives (Likert-type format: Not at all; Somewhat; Moderately; Very much; Absolutely) for evaluating a broad range of psychological symptoms, including anxiety and depression, over the past week [13]. The responses are summed up in the 'Global severity index'. A higher score on this index indicates more severe psychological symptoms or a higher number of psychological symptoms.

Personality-disorder characteristics

Personality-disorder characteristics were measured using the *Vragenlijst Kenmerken van Persoonlijkheid* (VKP), a Dutch self-report questionnaire based on the International Personality Disorder Examination [46]. The VKP is a validated and reliable self-report questionnaire with 197 questions and three fixed-response alternatives (true; ?; false) for assessing the presence of DSM-IV Axis II criteria of personality disorders over the past five years. 'Personality-disorder characteristics' were calculated by summing DSM-IV Axis II criteria, to which was responded with 'true'. A higher sum score indicates a higher number of DSM-IV Axis II criteria confirmed.

Presence of DSM-IV Axis I disorders in the past ('psychiatric history')

The presence of DSM-IV Axis I disorders, both currently and over their lifetime, was measured using the *Structured Clinical Interview for DSM-IV Axis I Disorders/Patient edition* (SCID-I/P) [55]. This is a semi-structured validated interview for classifying the major DSM-IV Axis I disorders. The presence of the DSM-IV Axis I disorders in the past ('psychiatric history') was calculated by summing the DSM-IV Axis I disorders in lifetime that were not currently present, and splitting the sum score into two categories (0: no DSM-IV Axis I disorders in the past; 1: one or more DSM-IV Axis I disorders in the past that were not currently present).

Health-related quality of life in the mental domain ('mental component summary')

Health-related quality of life in the mental domain was measured using the 'Mental Component Summary' (MCS) of the *36-item Medical Outcomes Study Short-Form General Health Survey* (SF-36) [168]. The MCS summarizes functional health and well-being in the mental domain over the past four weeks. This summary is transformed into T-scores with a mean of 50 and standard deviation of 10. A higher MCS-score indicates a better health-related quality of life in the mental domain.

Control variables

Pretreatment PCS scores, age, gender, marital status and employment status were used as control variables.

Statistical analyses

Required sample size

The randomized controlled trial on the effectiveness of the CBT group training resulted in a group of 162 patients. To verify whether this fixed number of patients was also sufficient for the present study, we applied a power analysis to calculate the sample size required for the present study [53; 102].

For this power analysis, the anticipated effect size of the set predictors was set at f^2=0.15 [34]. We decided that the predictor set should at least have this medium effect, because the predictors would exclude patients from treatment that had an exceptionally small risk of adverse events [65], and, also, because the selection and allocation assessment needed for this exclusion would raise costs. The desired statistical power level was set at 0.80 and the alpha at 0.05; both by convention [34]. The number of predictors was four. The predictors were selected on the basis of assumptions practiced in clinical practice. The number of control variables was five. The control variables were chosen on the basis of findings of other studies that indicated the potential relevance of these variables for CBT outcome. By selecting predictors used in clinical practice and by choosing control variables indicated by studies as potentially relevant, we reduced the number of predictors and control variables, and prevented 'fishing'.

A power analysis with these parameters led to a minimum required sample size of 113 patients [59; 139]. Adjusted for a dropout of 30 percent, this resulted in a total sample size of 161 patients. The total sample size of 162 patients in the randomized controlled trial was thus sufficient for the hierarchical multiple regression analyses of the present study.

Analyses

The statistical analyses concerned dropout and prediction. Drop-out analyses explored whether the patients who dropped out differed at baseline from the study completers (patients who could be followed over a year). This was analyzed using two-tailed t-tests for independent samples for the continuous variables, two-tailed Mann–Whitney U-tests for the ordinal variables, and chi-square tests for the categorical variables.

The prediction analyses included a preliminary exploration of the relationships between the individual predictors and CBT outcomes, and a full exploration of the predictive power of the predictor set while controlling for pretreatment score of the outcome measure and sociodemographic variables. For the preliminary exploration,

a correlation matrix was composed. For the full exploration, hierarchical multiple regression analyses were used. In the first step of these regression analyses, pretreatment score on the outcome measure and sociodemographic variables were simultaneously entered as a block to statistically control for their impact on CBT outcome. In the second step of these regression analyses, the predictors were simultaneously entered as a block to evaluate their impact as a set and as individual predictors on CBT outcome. Since predictors have clinical relevance only if they are stable over time, these analyses were conducted for immediate, short-term and long-term CBT outcomes.

Five checks were used to verify whether the assumptions of hierarchical multiple regression analysis had been met and how accurate the resulting model was [53; 117]. The first check used was the Cook's distance to explore whether the model was highly influenced by a small number of cases. The second check used was the tolerance to confirm non-multicollinearity. The third check used was the Durbin-Watson statistics to confirm the independency of errors. The fourth check used was the residual plots to explore linearity and homoscedasticity. The fifth check used was the Shapiro-Wilk test to confirm the normality of standardized residuals.

Results

Patients

Figure 7.1 shows the flow chart of patients through the study. The study started with 162 patients, 59 of whom dropped out.

Recruitment

The 59 patients who had dropped out of the study did not differ from the study completers with regard to their available scores for CBT outcome, control variables, and predictors (see Table 7.1), with the exception of a difference in the 'age' control variable. Patients who had dropped out were significantly younger (mean=42.4; SD=11.1; p=0.02) than the study completers (mean=46.7; SD=10.8).

With regard to the clinical characteristics shown in Table 7.2, no significant differences were found between the patients who had dropped out and the study completers.

Correlations between CBT outcomes, control variables, and predictors

Table 7.3 shows the correlation matrix between the CBT outcomes, the control variables, and the predictors. With regard to the control variables, the only control variable that predicted outcome consistently over time was the pretreatment PCS score. A lower pretreatment PCS score was associated with a better CBT outcome. The pretreatment PCS scores explained five to nine percent of the variance in CBT outcomes.

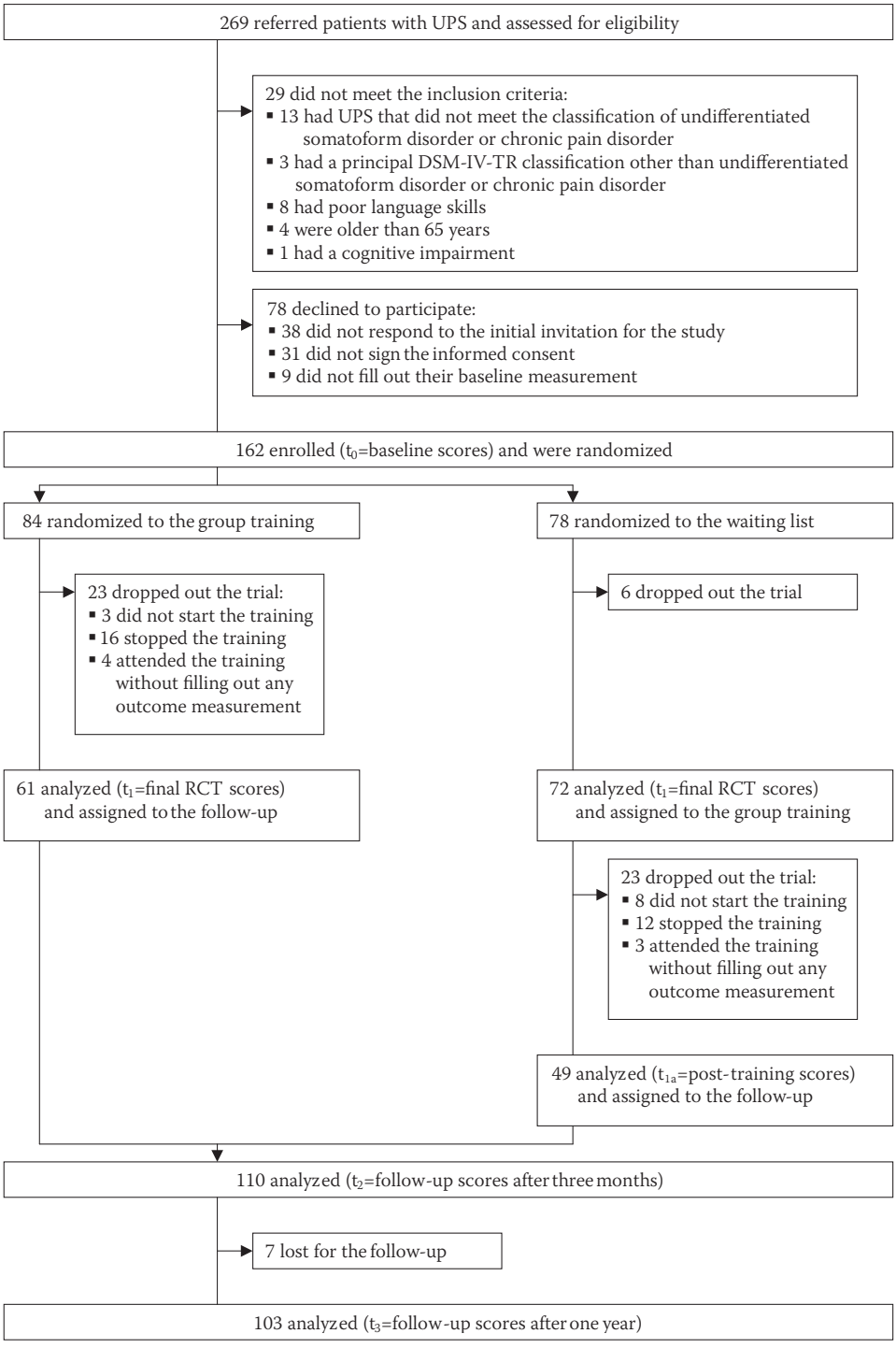


Figure 7.1. Patient flow

Table 7.1. Characteristics of CBT outcomes, control variables, and predictors

Characteristics			
CBT outcome	**n**	**mean**	**SD**
Immediate CBT outcome	102	4.49	7.59
Short-term CBT outcome	105	4.68	6.79
Long-term CBT outcome	98	5.03	7.55
Control variables	**n**	**mean**	**SD**
Physical Component Summary - PCS	158	29.20	8.97
Age in years	162	45.15	11.05
Gender, n *(%)*	162		
female		131	*(81%)*
male		31	*(19%)*
Marital status, n *(%)*	162		
married or living with a partner		110	*(68%)*
unmarried, divorced or widowed		52	*(32%)*
Employment, n *(%)*	162		
employed		57	*(35%)*
unemployed		105	*(65%)*
Predictors	**n**	**mean**	**SD**
Global severity index	161	165.36	50.28
Personality-disorder characteristics	160	15.07	12.96
Psychiatric history, n *(%)*	162		
presence of a psychiatric history		68	*(42%)*
absence of a psychiatric history		94	*(58%)*
Mental Component Summary - MCS	158	45.15	11.89

Table 7.2. Clinical characteristics

Clinical characteristic	**n=162**
Duration of UPS in years, median *(interquartile range)*	9 *(3-16)*
Classification of UPS by SCID-I/P	
undifferentiated somatoform disorder	63
chronic pain disorder	99
Number of comorbid DSM-IV Axis I disorders	
no comorbid DSM-IV Axis I disorder	95
one comorbid DSM-IV Axis I disorder	43
two comorbid DSM-IV Axis I disorders	17
three comorbid DSM-IV Axis I disorders	4
four or more comorbid DSM-IV Axis I disorders	3
Classification of comorbid DSM-IV Axis I disorder	
mood disorder (in past; in lifetime)	24 (46;70)
anxiety disorder (in past; in lifetime)	47 (30;77)
substance-related disorder (in past; in lifetime)	1 (17;18)
eating disorder (in past; in lifetime)	1 (5;6)

psychotic disorder (in past; in lifetime)	0 (1;1)
other somatoform disorder	26
adjustment disorder	4
other disorder (in past; in lifetime)	1 (0;1)
Number of comorbid DSM-IV Axis II disorders	
no comorbid DSM-IV Axis II disorder	113
one comorbid DSM-IV Axis II disorder	27
two comorbid DSM-IV Axis II disorders	10
three or more comorbid DSM-IV Axis II disorders	10
missing	2
Classification of comorbid DSM-IV Axis II disorder	
paranoid personality disorder	18
schizoid personality disorder	5
schizotypal personality disorder	2
anti-social personality disorder	1
borderline personality disorder	7
histrionic personality disorder	2
narcissistic personality disorder	2
avoidant personality disorder	29
dependent personality disorder	4
obsessive compulsive personality disorder	24
Psychiatric history (number of *past* DSM-IV Axis I disorders)	
no *past* DSM-IV Axis I disorder	94
one *past* DSM-IV Axis I disorder	46
two *past* DSM-IV Axis I disorders	17
three *past* DSM-IV Axis I disorders	3
four or more *past* DSM-IV Axis I disorders	2
Referrer	
primary medical service	82
secondary medical service	51
secondary mental service	29

With regard to the predictors, no predictor predicted outcome consistently over time. The correlations between the predictors and the CBT outcomes were rather low according to Cohen's guidelines [34]. Only the pretreatment MCS scores were significantly correlated with CBT short-term outcome. Higher pretreatment MCS scores were associated with better CBT short-term outcome. These pretreatment MCS scores explained six percent of the variance in the short-term CBT outcome.

Table 7.3. Correlation matrix with CBT outcomes, control variables and predictors

	CBT outcome		
	Immediate	**Short-term**	**Long-term**
CBT outcome			
Immediate CBT outcome	1.00		
Short-term CBT outcome	.60***	1.00	
Long-term CBT outcome	.58***	.58***	1.00
Control variables			
Physical Component Summary (SF-36: PCS)	-.30**	-.24*	-.22*
Age	-.03	.05	-.15
Gender	-.02	-.01	.04
Marital status	.07	-.02	.06
Employment	-.07	-.08	.07
Predictors			
Global severity index (SCL-90-R)	.11	.01	.10
Personality-disorder characteristics (VKP)	-.04	-.17	-.11
Psychiatric history (SCID-I/P)	-.01	.13	-.01
Mental Component Summary (SF-36: MCS)	.19	.25**	.11

*p≦0.05, **p≦0.01, ***p≦0.001.

Prediction of immediate, short-term and long-term CBT outcome

Table 7.4 shows the hierarchical multiple regression models for predicting CBT outcome. The complete model was able to predict immediate CBT outcome ($F(9, 92)=2.12$; $p=0.04$) and short-term CBT outcome ($F(9,95)=2.85$; $p=0.005$); but not long-term CBT outcome ($F(9, 88)=1.81$; $p=0.08$). When the effects of pretreatment outcome scores and sociodemographic variables were statistically controlled, the predictor set was only able to predict short-term CBT outcome ($F(4,95)=4.41$; $p=0.003$); but not immediate CBT outcome ($F(4,92)=0.17$; $p=0.17$) and long-term CBT outcome ($F(4,88)=1.54$; $p=0.20$). The resulting explained variance in CBT outcome was 6% at the end of CBT, 15% at three-month follow-up, and 6% at one-year follow-up. For short-term CBT outcome, a better outcome was predicted by more psychological symptoms, fewer personality-disorder characteristics, the presence of a psychiatric history, and a better quality of life in the mental domain. There were no indications that the models were highly influenced by a small number of cases or by violating the assumptions of hierarchical multiple regressions analysis.

Table 7.4. Hierarchical multiple regression models for predicting CBT outcome

	Immediate CBT outcome[1]				Short-term CBT outcome[2]				Long-term CBT outcome[3]			
	b	Standard error	β [4]	R^2	b	Standard error	β[4]	R^2	b	Standard error	β[4]	R^2
Step 1												
Constant	13.10	4.10			9.09	3.72			14.88	4.38		
Control variables												
Physical Component Summary (SF-36: PCS)	-0.27	0.08	-.34**		-0.19	0.08	-.26*		-0.22	0.08	-.27*	
Age	-0.05	0.07	-.07		0.03	0.07	.04		-0.11	0.08	-.16	
Gender	2.33	2.02	.12		1.09	1.79	.06		2.66	2.11	.13	
Marital status	1.60	1.65	.10		-0.49	1.51	-.03		1.39	1.66	.09	
Employment	-0.36	1.69	-.02		-0.16	1.51	-.01		1.26	1.73	.08	
Explained variance by control variables (R2)				.11				.07				.10
Step 2												
Constant	-10.06	10.22			-12.36	8.24			0.87	10.57		
Control variables												
Physical Component Summary (SF-36: PCS)	-0.16	0.09	-.20		-0.10	0.08	-.13		-0.15	0.09	-.19	
Age	-0.01	0.07	-.02		0.04	0.06	.06		-0.10	0.08	-.14	
Gender	1.05	2.20	.05		0.92	1.89	.05		1.51	2.32	.07	
Marital status	1.85	1.65	.11		-0.42	1.42	-.03		1.25	1.66	.08	
Employment	-0.53	1.68	-.03		-0.71	1.43	-.05		1.06	1.73	.06	
Predictors												
Global severity index (SCL-90-R)	0.06	0.03	.36*		0.06	0.02	.41**		0.06	0.03	.33*	
Personality-disorder characteristics (VKP)	-0.08	0.09	-.11		-0.19	0.07	-.32*		-0.18	0.09	-.28*	
Psychiatric history (SCID/P)	0.72	1.50	.05		2.79	1.27	.20*		1.12	1.52	.07	
Mental Component Summary (SF-36: MCS)	0.20	0.09	.30*		0.21	0.07	.36**		0.10	0.09	.15	
Explained variance by predictors (ΔR2)				.06				.15**				.06

[1]Immediate CBT outcome was computed by subtracting the baseline PCS-score from the post-training PCS-score.
[2]Short-term CBT outcome was computed by subtracting the baseline PCS-score from the three-months follow-up PCS-score.
[3]Long-term CBT outcome was computed by subtracting the baseline PCS-score from the one-year follow-up PCS-score.
[4]β is the standardized value of b.
*p≦0.05, **p≦0.01, ***p≦0.001.

Discussion

Principal findings

We explored whether psychological symptoms, personality-disorder characteristics, psychiatric history, and health-related quality of life in the mental domain assessed at baseline predicted CBT outcome at the end of CBT (immediate outcome), three months after CBT (short-term outcome) and one year after CBT (long-term outcome), after control for pretreatment scores on the outcome measure and for sociodemographic variables. We found that these predictors in combination with the control variables significantly predicted the immediate and short-term outcome of CBT, but not the long-term outcome.

The predictor set alone was significantly associated only with short-term CBT outcome. At this time-point, all predictors were significant. Psychological symptoms had the strongest association with short-term outcome followed by – in descending order of strength – health-related quality of life in the mental domain, personality-disorder characteristics, and psychiatric history. Psychological symptoms, health-related quality of life in the mental domain, and psychiatric history were positively associated with short-term outcome, meaning that a better outcome was expected if the number of psychological symptoms had been higher at baseline, if quality of life had been better at baseline, and if a psychiatric history had been present at baseline. Personality-disorder characteristics were negatively associated with short-term outcome, meaning a better outcome was expected if the number of personality-disorder characteristics had been lower at baseline.

As the predictor set did not significantly predict outcome at all three time points, its effects were not stable over time. This instability makes it unsuitable for selection and allocation of patients to CBT.

Our principal findings in relation to the existing literature

The finding that effects of predictors were not stable over time was consistent with the findings of other studies [16; 19; 20; 33; 39; 60; 69; 77; 95; 96; 101; 107; 121; 125; 132] that have investigated the association between psychiatric comorbidity and treatment outcome, and showed no stability of predictors between studies or over time within studies. However, unlike these studies [16; 19; 33], our own study controlled statistically for the effects of pretreatment score on the outcome measure and sociodemographic variables. Even under these conditions, predictors still did not consistently predict which patients benefited from CBT and which did not.

The possible reasons for the inconsistent findings over studies on predictor effects might be that the study groups were too small or the group of patients with UPS studied was too heterogeneous. Other reasons might be that the sets of predictors in the studies

were wrongly measured and/or chosen. Predicting CBT outcome might be more complex, and may require a larger set of variables than the sets of predictors which were investigated in the studies. For instance, it may require a good match between trainer and trainees, a supportive but not over-protective partner, no deaths nearby, no moving house, and no termination of employment. It has been estimated that factors in client-therapist relationship account for 30% of treatment outcome, and factors outside CBT for another 40% [92].

Strengths and limitations in the study

The strength of the present study was that the impact of a predictor set on the primary outcome measure was explored at three time points over one year after CBT [111]. As most other studies were designed to predict treatment outcome at only one time point after CBT [19; 95; 107; 132], they did not explore the stability of the predictor effect over time. They also used more than one outcome measure without indicating the primary outcome measure [16; 19; 95; 121]. By this, other studies did not explore the stability of predictor effects over time on the outcome measure that was preliminary chosen as the most important outcome of CBT.

A limitation of the study was that personality-disorder characteristics were measured using a self-report questionnaire. Although many patients met the DSM-IV Axis II criteria for the classification of a specific personality-disorder subtype, only two met the general criteria applying to all personality disorders. Patients seemed to view any maladaptive thoughts, feelings and behavior associated with personal and social disruption as a specific reaction to a situation rather than a pervasive and stable pattern across many situations. If these reactions were indeed determined by a specific situation, our classification of a personality disorder would have been incorrect. However, a high number of personality disorders was to be expected: our patients had had their UPS for an average of nine years, and the prevalence of personality disorders in such patients is four times higher than in the healthy population [108]. The total number of DSM-IV Axis II criteria confirmed in our study (mean=15.07; SD=12.96) was significantly larger than the one in the 'normal population' reference group (mean=12.54; SD=9.79), and significantly less than the one in the 'psychiatric patients' reference group (mean=25.37; SD=13.55) [46]. The validity problem caused by the failure to meet the general criteria applicable to all personality disorders might be partially solved by using structured interviews. Although this might provide a more objective perspective, it still depends on information communicated by patients and also on patients' views of their own thoughts, feelings and behavior.

Clinical and policy implications

In routine practice assessments, patients with UPS are selected and allocated to different kinds of treatment on the basis of psychological symptoms, personality-disorder characteristics, psychiatric history, and health-related quality of life. As the prevalence of comorbid mood, anxiety [67], and personality disorders [108] is high in this patient group, patients are often redirected from treatment for UPS to treatment for mental health problems, which is usually provided by the mental health services. However, these predictors did not consistently predict CBT outcome, neither in our study nor in our review of other studies, and as a substantial number of patients communicates in physical and not mental terms [120] and refuses to be referred to the mental health services [5; 122], this practice does not seem to be appropriate.

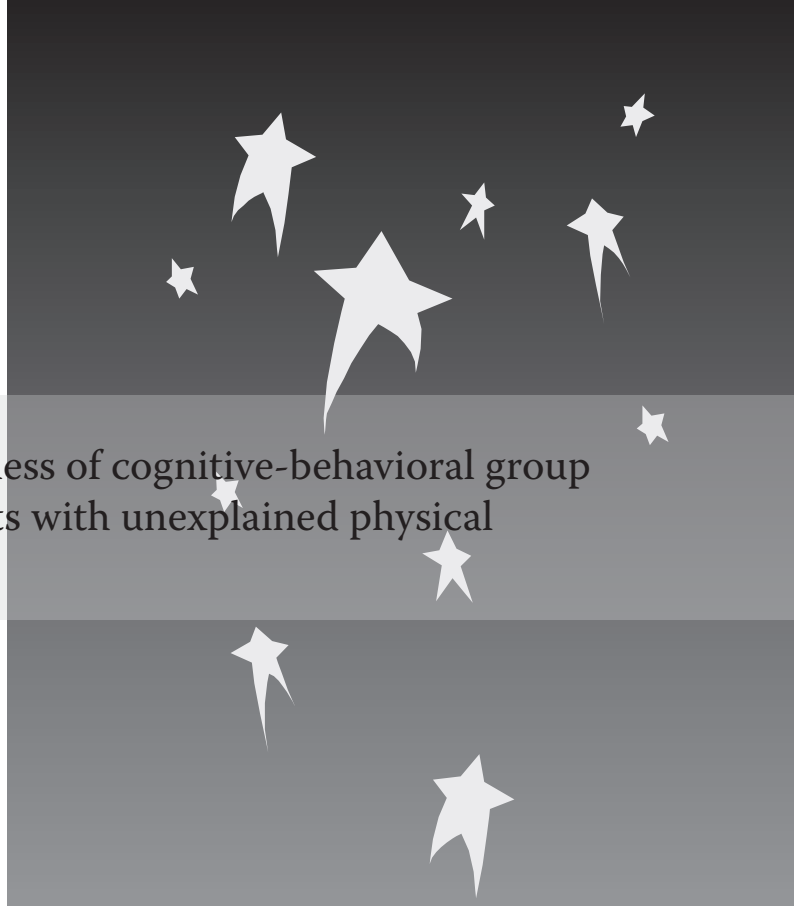
Conclusions

As psychological symptoms, personality-disorder characteristics, psychiatric history, and health-related quality of life in the mental domain assessed at baseline did not seem to predict CBT outcome consistently over time, the need for selection and allocation of patients on the basis of these variables to CBT is doubtful. In our study, if patients had been excluded from CBT on the basis of these variables, they would have been deprived unnecessarily of effective group training.

Chapter

7

Chapter 8



The cost-effectiveness of cognitive-behavioral group training for patients with unexplained physical symptoms

Abstract

Background

The aim of this study was to evaluate the cost-effectiveness of a cognitive-behavioral group training compared with a waiting list for patients with Unexplained Physical Symptoms (UPS).

Methods

A probabilistic decision-analytic model existing of three health states (Poor Health, Average Health and Death) was built based on a cut-off score on the physical component summary of the SF-36. To assess the cost-effectiveness in terms of cost per Quality Adjusted Life Year (QALY), a societal perspective was adapted with cycles of three months and a time horizon of four years. Data for the model were derived from a study, in which 162 patients with UPS were randomized either to the treatment group or to the waiting list. Data were assessed at baseline, after the training or the waiting list, at three months after the training and at one year after the training.

Results

After four years, the group training was dominant with a negative incremental cost-effective ratio of -€16,892 per QALY compared with the waiting list. The cost-effectiveness improved with a longer time horizon. The threshold of €30,000 per QALY was passed after 18 months and €0 per QALY after 30 months.

Conclusion

The cognitive-behavioral group training is a cost-effective treatment compared with the waiting list in patients with UPS.

Background

Unexplained Physical Symptoms (UPS) are physical symptoms that cannot be fully explained on the basis of a known medical condition. These symptoms can be classified as a DSM-IV somatoform disorder if they a) are not intentionally produced or feigned, b) cause clinically significant distress or impairment in functioning, c) persist at least six months, and d) are not better accounted for by other DSM-IV classifications. Somatoform disorders are common in primary care. Their prevalence ranges from four (without the prevalence of undifferentiated somatoform disorder and body dysmorphic disorder) [58] to 16% (without prevalence of somatoform disorder not otherwise specified) [38]. By definition, somatoform disorders are accompanied by high levels of psychosocial distress and/or impairment resulting in lost labor-force and household productivity [124], and in a high use of healthcare services [14; 15]. The high prevalence rate of UPS combined with its high costs make UPS not only a considerable burden for patients but also an economic burden for society [14; 124; 135].

Research indicates that cognitive-behavioral therapy is the most effective therapy for UPS [86; 152], but research into the cost-effectiveness of this therapy is scarce and has methodological limitations. A recent systematic literature review [80] identified eight economic evaluations of treatments for UPS, of which only two investigated the cost-effectiveness by explicitly combining differences in costs with differences in effects into incremental cost-effectiveness ratios (the ratio of additional costs and additional effects). However, even these studies did not employ a state-of-the-art cost-effectiveness research design, as they did not include costs due to productivity losses, they applied a time horizon limited to one year [130] or to three months [106], and they used disease specific effects such as 'cost per unit reduction in Health Anxiety Inventory score' [130] and 'cost per additional successfully treated patient' [106]. The use of such specific effect measures complicates not only the comparisons of the cost-effectiveness ratios of different treatments within the same disease, but also the ones between different diseases, such as comparing the cost-effectiveness ratios of treatments for UPS with those of treatments for diabetes. When these comparisons of cost-effectiveness ratios are favorable to treatments for UPS, one would have a strong argument to reimburse treatment of UPS similar to diseases with a known medical diagnosis. Such comparisons require the use of generic effect variables like costs per Quality Adjusted Life Year (QALY), which is the preferred outcome in health economics [44].

In health economics, one tries to incorporate all costs and effects, even if the costs and effects occur in the future [44]. Future costs and effects are for instance important if one claims that the initial investment in the treatment is offset by future saving in healthcare costs elsewhere. A state-of-the-art health economic model which estimates further costs and effects while controlling for statistical uncertainty and design assumptions is the

multivariate probabilistic model [28]. We evaluated the cost-effectiveness of a cognitive-behavioral group training compared with a waiting list for patients with UPS using such a state-of-the-art health economic model.

Methods

Design

The data for this study emerged from a randomized controlled trial with a non-randomized one-year follow-up investigating the effectiveness of cognitive-behavioral group training for patients with UPS [175]. In the trial, patients were randomized either to the group training (training group 1) or to a waiting list after completing the baseline measurement (T_0). The effect of the group training was measured three months later directly after the training (T_1), or after the same period for those on the waiting list (T_1). After T_1, patients on the waiting list also attended the training (training group 2), by which their T_1 became their 'repeated T_0', and, as they were also assessed directly after their training, a 'new T_1' measurement for them was created. In the follow-up, the outcome was measured at three months after the end of the training (T_2) and once again at one year after the end of the training (T_3). The study was approved by the Erasmus Medical Research Ethics Committee, and registered in the Dutch Trial Register (NTR 1609) [171]. A detailed description of the study protocol can be found in Chapter 3, and has been published elsewhere [173].

Participants

Participants were recruited in different healthcare centers in the Rotterdam area in the Netherlands. General practitioners and specialists were asked to refer patients aged between 18 and 65 years whose physical symptoms, according to their clinical judgment, could not be explained on the basis of a known medical condition. Patients were included if they signed the informed consent and if their UPS fulfilled the DSM-IV criteria for an undifferentiated somatoform disorder or a chronic pain disorder. To verify whether UPS fulfilled these DSM-IV criteria, we used the *Structured Clinical Interview for DSM-IV Axis I Disorders/Patient edition* (SCID-I/P) [55], a semi-structured validated interview for making the major DSM-IV Axis I diagnoses. Patients were excluded if poor language skills or handicaps, such as cognitive impairment, prevented them from understanding the cognitive-behavioral group training. Table 8.1 shows the patients' baseline characteristics.

Table 8.1. Baseline characteristics

Patients' characteristic	Group training (n=84)	Waiting list (n=78)
Age in years, mean	46	44
Gender, % female	80%	82%
Physical Component Summary (PCS), mean	29.34	29.05
Mental Component Summary (MCS), mean	43.68	46.72
Duration of UPS in years, median	8	9.5
Classification of comorbid DSM-IV Axis I disorders measured by SCID-I/P		
mood disorder (lifetime)	13 (40)	11 (30)
anxiety disorder (lifetime)	20 (36)	27 (41)
substance-related disorder (lifetime)	1 (12)	0 (6)
eating disorder (lifetime)	1 (4)	0 (2)
psychotic disorder (lifetime)	0 (0)	0 (1)
somatization disorder	14	10
hypochondriasis	1	1
adjustment disorder	2	2

Cognitive-behavioral group training

The intervention is the cognitive-behavioral group training called 'Coping with the consequences of unexplained physical symptoms'. This weekly two-hour manual-based [170] training is held over a three-months period. The group training starts with a minimum of five and a maximum of ten patients. The aim of the group training is to improve health-related quality of life. Corresponding to this aim, the primary outcome measures in the randomized controlled trial were the two component summaries of the *36-item Medical Outcomes Study Short-Form General Health Survey* (SF-36) [168]: 'Physical Component Summary' (PCS) and 'Mental Component Summary' (MCS). More details of the group training can be found in Chapters 3-5 and have been published elsewhere [172-174]. The effectiveness of the group training is described in Chapter 6 and has been published elsewhere [175].

Cost-effectiveness

The design of the present study provided empirical data of the costs and effects of the group training and the waiting list over a period of three months, after which patients on the waiting list attended the training and all treated patients were followed one year after the group training. However, it is to be expected that the effect will sustain longer than these periods. We therefore developed a Markov cohort model [28], in which we simulated a cohort of patients that moved through health states over time, up till four years.

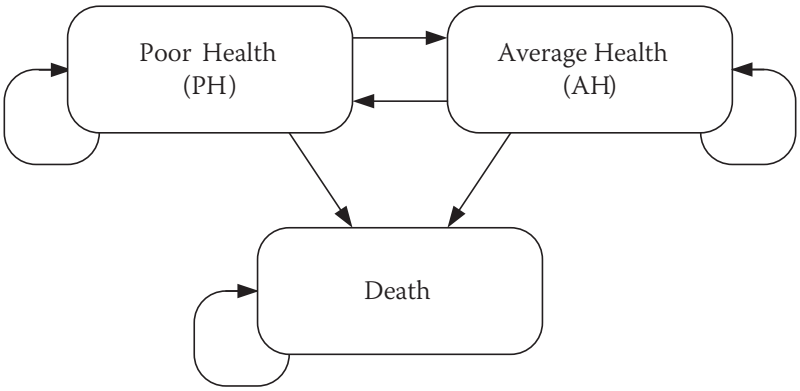


Figure 8.1. State transition diagram of the Markov model for UPS

In the present study, only PCS as primary outcome measure was used, because patients reported the quality of life in the physical domain as most burdensome and PCS had shown to be a sensitive parameter for the effects of the group training [175]. As Figure 8.1 shows, our Markov cohort model defined three fixed mutual exclusive health states: Average Health (AH), Poor Health (PH) and Death. To define AH and PH, a cut-off score of 40 on the PCS was used, as the score of 40 was in the middle of the scores of the general population (mean=50; SD=10) and the scores of our patient group (mean=29; SD=9). AH represented patients with scores higher than 40 on the PCS, and PH represented patients with scores lower than 40.

The variation over time in the effects and in the costs within the health states AH and PH was tested and assumed to be constant over time. The length of the Markov cycles was chosen to be three months, so that the three months of the training could be easily accommodated. To acknowledge the uncertainty of the long-term effects, we used a time horizon of four years and not an infinite time horizon as baseline scenario. Although an infinite time horizon would align with health-economic guidelines [44], it would also assume that we know that the effects sustain well beyond four years. This might be considered an unrealistic assumption, given that we only had three-months data to compare the effects of the group training with those of the waiting list. As we do not know how long effects might sustain, we were also interested in the minimal time horizon needed to show acceptable cost-effectiveness. Both the mean age of the simulated patient cohort in the model (45 years) and the distribution of patients over health states (AH=11%; PH=89%) at the start of the model were derived from the trial data at baseline (T_0). Costs per patient will depend on the number of participants per training: more participants would mean lower cost per patient, under the assumption of similar effects. The average number of participants per training in de model was six patients.

Transition probabilities

In order to allow transitions between health states (getting better or getting worse), a probability of switching to another health state or staying in the same health state was assigned to each health state, based on study data (Table 8.2). In the present study, such data for the waiting list condition were only available in the first cycle (T_0- T_1). After this cycle, the transition probabilities for the waiting list condition were assumed to be constant but flexible, as the same number of patients on the waiting list switched between the health states. For the training condition, the transition probabilities for the first cycle were estimated using the T_0- T_1 data of the training group 1 (the original 'experimental' training group) combined with the new 'T_0- T_1' data of training group 2 (the original waiting list group). The transition probabilities after attending the training were estimated using data T_1 through T_3, and assumed to be constant after T_3. At T_0, there were nine patients of the waiting list condition in health state AH, and none of them deteriorated to the health state PH in the first cycle, while two patients improved from PH to AH. Given the chronic character of UPS in our sample - median duration of UPS was nine years -, it is unlikely that a zero chance of deterioration for patients on the waiting list in the health state AH would be a valid estimate. It might be more likely that deterioration and improvement in the waiting list condition were in balance. We therefore assumed 'transition balance', in which the probabilities were estimated in such

Table 8.2. Transition probabilities

Transition	Cycle 1			Cycle 2			Cycle 3-5		
	Mean	SE	N	Mean	SE	N	Mean	SE	N
Group training [1]									
Improve (from PH to AH)[2]	0.18	0.041	16	0.11	0.037	8	0.04	0.023	7
Stay in PH	0.82	[4]	71	0.89	[4]	64	0.96	[4]	60
Relapse (from AH to PH)	0.17	0.103	2	0.32	0.091	8	0.14	0.066	10
Stay in AH	0.83	[5]	10	0.68	[5]	17	0.86	[5]	17
Waiting list [3]									
Improve (from PH to AH)	0.04	0.024	2						
Stay in PH	0.96	[4]	55						
Relapse (from AH to PH)	0.29[6]	0.044[6]	(0[7])[6]						
Stay in AH	0.71[6]	[5]	(9[7])[6]						

[1] In the calculations, training group 1 and 2 were used.
[2] PH = Poor Health; AH = Average Health.
[3] In the waiting list group, only transitions in the first cycle were measured and extrapolated to the other cycles in the model.
[4] The standard error of the 'Stay in PH' state is equal to the 'Improve' state as the mean is 1 minus 'Improve'.
[5] The standard error of the 'Stay in AH' state is equal to the 'Relapse' state as the mean is 1 minus 'Relapse'.
[6] This was based on 'transition balance'.
[7] This was the original N, which wasn't used in the model because of the zero transition in relapse.

a way that the number of transitions going in different directions during the waiting list was equal.

The mortality figures were derived from the Dutch death register in 2010 provided by Statistics Netherlands CBS [147]. It included an average death risk depending on age for both men and women but not for patients with UPS specifically. We assumed the same mortality for both AH and PH patients.

Costs

The costs of the group training were calculated on the basis of a local cost study (see Table 8.3). The cost study included the estimation of the volume and cost prices of personnel, overhead, material, housing, training and retraining of personnel, recruitment and travel. Time cost of patients following the group training was not measured, because only 45% of the patients was working of whom 48% worked 24 hours or less. These values were measured using the TiC-P questionnaire, further explained below. Furthermore, patients had the opportunity to follow the training outside working hours.

Table 8.3. Costs per training

Category	Cost in €
Personnel	7,587
Overhead	2,509
Material	131
Housing	1,050
Training and retraining[1)]	20
Recruitment	15
Travel	20
Total cost	**12,275**
Total cost per patient	**2,012**

[1)] Average per training.

To estimate medical costs other than the group training, we used the 2002 version of the *Trimbos/iMTA Questionnaire for Costs associated with Psychiatric Illness* (TiC-P), a self-report questionnaire for assessing healthcare-related and work-related costs of illness. The TiC-P has 29 questions and semi-fixed-response alternatives [23; 62]. The first part of the TiC-P measures the healthcare-related costs incurred through the use of healthcare services and medications over the past four weeks. The second part of TiC-P, which is based on the short form of the Health and Labour Questionnaire, measures the work-related costs over the past two weeks caused by absenteeism (the absence from work), presenteeism (a reduced efficiency at work), and substitution of domestic tasks.

The health states were fixed and assumed to be constant over time. Therefore, an average of the cost scores was used per cycle for the health states. This assumption was

supported by the constant flat distribution of costs over time, which can be observed in Table 8.4. Costs were discounted at 4% and represented 2011 cost prices.

Table 8.4. Healthcare-related and work-related costs per cycle

Costs	T_1 [1]		T_2 [2]		T_3 [2]		Average [3]	
	PH N=134	AH N=36	PH N=79	AH N=28	PH N=72	AH N=27	PH N=285	AH N=91
Healthcare-related costs in €								
Medication costs	49	15	54	18	48	24	50	19
Other healthcare-related costs	1,090	612	1,569	594	1,699	531	1,376	583
Work-related costs in €								
Absenteeism	618	32	329	190	619	-	539	71
Presenteeism	338	40	174	-	91	16	230	21
Substitution of domestic tasks	450	72	440	39	532	11	469	43

[1] In the calculations, the T_1 of training group 1, 'new T_1' of training group 2 and T_1 of waiting list group were used.
[2] In the calculations, the T_1 of training group 1 and 'new T_1' of training group 2 were used.
[3] For the model, the average values were used.

QALYs

The effects were expressed in terms of QALYs. The quality of life weights needed to estimate the QALYs (the so-called 'utilities') were extracted from the SF-36 [168]. Eleven of the 36 items of this self-report questionnaire are converted into six dimensions ('SF-6D'): physical functioning, role limitations, social functioning, pain, mental health, and vitality [26]. Like costs, utilities were assumed to be constant over time and therefore an average of the utility scores was used per cycle for the health states. This assumption was supported by the constant distribution over time which can be observed in Table 8.5. Like costs, the effects were discounted at a rate of 4% per year.

Table 8.5. Utilities

Health state	Baseline	T_1 [1]	T_2	T_3	Average [2]
Poor Health (PH)					
Mean (SE)	0.57 (0.007)	0.57 (0.007)	0.58 (0.011)	0.58 (0.012)	0.578 (0.004)
Average Health (AH)					
Mean (SE)	0.69 (0.025)	0.70 (0.016)	0.74 (0.018)	0.73 (0.022)	0.715 (0.010)

[1] In the calculations, the 'new T_1' of training group 2 was also used.
[2] For the model, the average values were used.

Analysis

Since this study involved synthesizing data from a number of sources with different forms of sampling errors and with different assumptions, it is important to assess the uncertainties in the model in a multivariate way and under varying assumptions. Multivariate probabilistic sensitivity analysis of the uncertainty of parameters (that

is the uncertainty which relates to sampling error) was undertaken by a Monte Carlo simulation. The parameters included the transition probabilities, the costs and the QALYs. Since the costs were skewed, gamma distributions were used for the costs in the model. Ten thousand simulations were conducted, in which parameter values for transition probabilities, costs and QALYs were randomly sampled from their distribution. This resulted in 10,000 unique sets of parameters, which were used in the model to calculate the expected costs and QALYs of a cohort of 1,000 patients in the training condition and a cohort of 1,000 patients on a 'four-years waiting list' condition. The resulting costs and effects were combined to calculate 10,000 Incremental Cost-Effectiveness Ratios (ICERs). These 10,000 ICERs were plotted in an ICER scatterplot. When ICERs are in the bottom right quarter of the scatterplot, the training is dominant, i.e. cost saving and QALY improving. When ICERs are in the top left quarter, the training costs more, and does not improve health. For ICERs in the top right quarter, a trade-off should be made between costs and effects, so a threshold is needed, i.e. how much is society willing to pay for additional health? The societal Willingness To Pay (WTP) level was set at €30,000 per gained QALY, which roughly reflects an accepted WTP level in the Netherlands [150].

Furthermore, a Cost-Effectiveness Acceptability Curve (CEAC) was created. The CEAC indicates the probability that the intervention under evaluation will be cost-effective at different values of WTP for a QALY. By definition, a CEAC crosses the Y-axis at the probability that the intervention is cost neutral: the WTP is then zero [51].

To get more insight in the development of the cost-effectiveness over time, we also plotted the ICER after each cycle. As described before, the effects of the training on the training group 2 (the waiting list group) were combined with those on the training group 1. One could argue that the new 'T_0-T_1' data may not represent the effect on which the randomized controlled trial was based (for instance because the waiting time had also an effect). Therefore, we tested the accuracy of this bundling of data in a sensitivity analysis, in which we used only data from training group 1. Also, we plotted the ICER when excluding the effect data of the training group 2.

Results

The mean four-year costs and health outcomes are presented in Table 8.6. The table shows that the training group had lower mean costs than the waiting list group, suggesting the costs of training were offset with savings elsewhere. When looking at the QALYs, the training group had a higher number of mean QALYs than the waiting list group, suggesting a small benefit of the training. After four years, the training showed better effects against lower costs in comparison to the waiting list. The group training resulted in a negative ICER of -€16,892 per QALY compared with the waiting list.

Table 8.6. Discounted costs and health outcomes over four years

Group	Costs in €	QALYs	ICER in €[1)]	Average Health (%)[2)]
Group training	33,906	2.25	-16,892	14.0
Waiting list	34,957	2.19	-	10.8

[1)] ICER = Incremental Cost-Effectiveness Ratio.
[2)] Percentage of participants in the Average Health state at four years.

The impact of parameters' uncertainty on the ICERs is shown in Figure 8.2, in which the results of the 10,000 probabilistic simulations are plotted in an ICER scatterplot. This scatterplot shows the differences in costs and QALYs per simulation, per patient between the group training and the waiting list. Around 75% of the simulations ended up below the X-axis, which means cost saving and QALY improving. Approximately 90% of the simulations were below the threshold of €30,000 per gained QALY, which means that the costs for improvement were within the borders that society is willing to pay for additional health (WTP). The increase in QALYs seemed to be modest; smaller than 0.18 over four years. However, as almost all simulations ended up at the right side of the Y-axis, improvement appeared with high certainty.

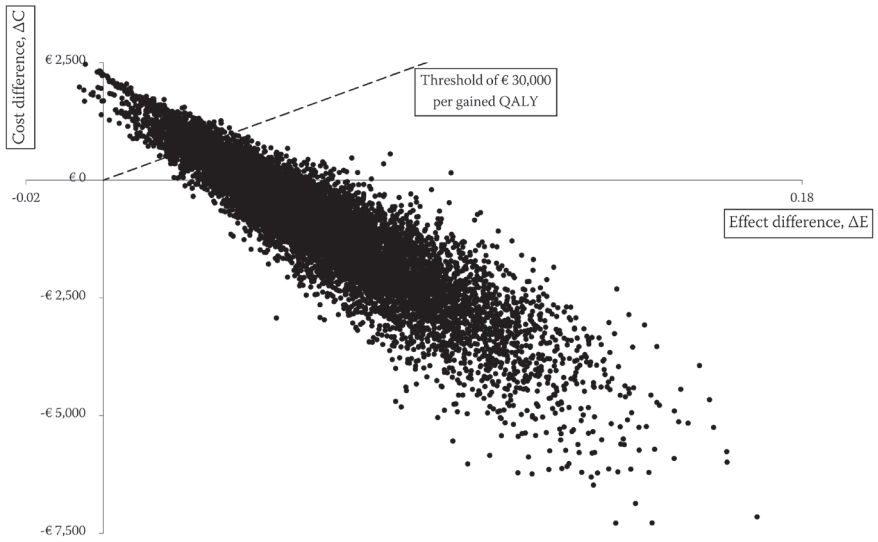


Figure 8.2. Incremental Cost-Effectiveness Ratio (ICER) scatterplot

Figure 8.3 indicates the probability that the cognitive-behavioral group training will be cost-effective at different values of WTP for a QALY. The CEAC for the group training crossed the Y-axis at the probability of 0.75, which means that the group training was cost-saving in approximately 75% of the simulations; the WTP was then zero. This indicated a high certainty that the costs will reduce over time after the group training.

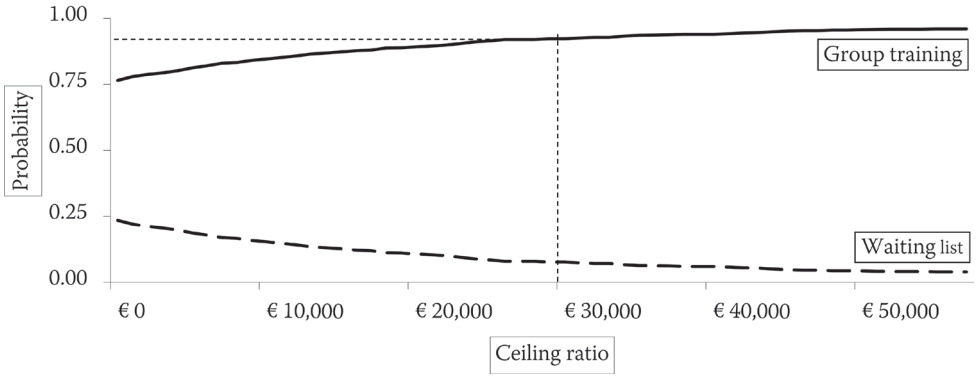


Figure 8.3. Cost-Effectiveness Acceptability Curve (CEAC)

If society is willing to pay €30,000 per QALY, the chance that the group training was a more cost-effective option than a waiting list was 90%. To say it differently: If society is willing to pay €30,000 per QALY, the chance that the waiting list will be the most cost-effective option, was only 10%.

Figure 8.4 reflects the uncertainty of the ICERs over time, and also includes the ICERs when excluding the effect data of training group 2. After 18 months (six cycles), the cost of a gained QALY due to the group training was less than €30,000. After 30 months (ten cycles), the cost of a gained QALY due to the group training was zero. When using only data from training group 1, comparable results were found.

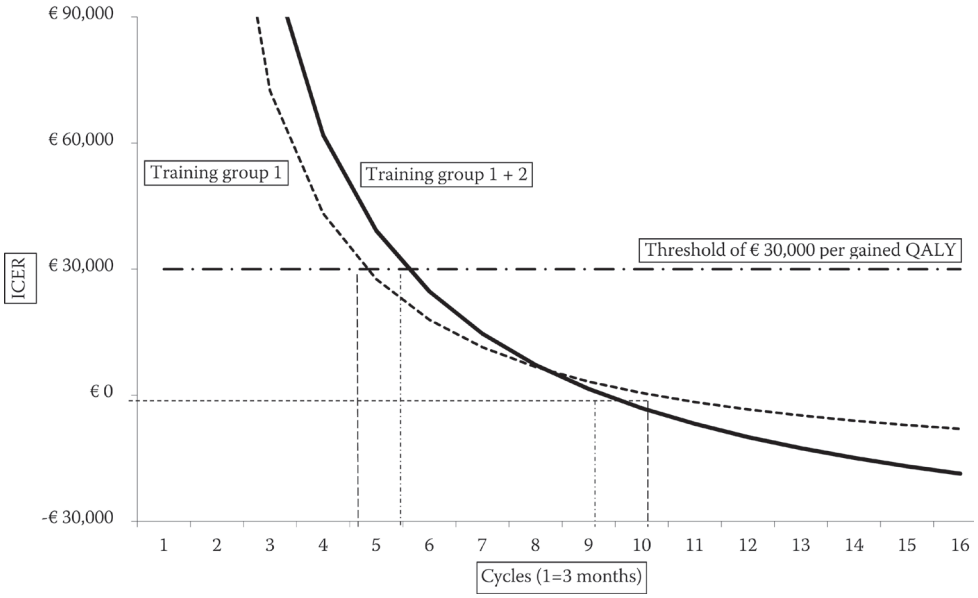


Figure 8.4. Incremental Cost-Effectiveness Ratio (ICER) over time

Discussion

Principal findings

We estimated the cost-effectiveness of cognitive-behavioral group training for patients with UPS over a four-year time horizon using a multivariate probabilistic model. After four years, the group training had a better effect on health-related quality of life and lower costs from a societal perspective than the waiting list. The group training resulted in an ICER of -€16,892 per QALY. After 30 months, the effect of the cognitive-behavioral group training was cost saving. If society is willing to pay €30,000 per gained QALY, then the group training was cost-effective after 18 months. This is almost the time of the end of the study period (15 months), which indicates that only a small amount of extrapolation of costs, effects and transition data was needed in the group training before a reasonable cost-effectiveness was reached. Using a time horizon of four years and assuming no willingness to pay for gained QALYs, the chance that the training will be the most-cost effective option was 75%.

Our principal findings in relation to the existing literature

This study is one of the few cost-effectiveness studies in patients with UPS, and the first to use a state-of-the-art health economic model and the preferred outcome in health economics: QALYs. To the best of our knowledge, only two studies investigated the cost-effectiveness of treatment for patients with UPS using cost-effectiveness ratios [80]. However, as these studies used specific outcome 'cost per unit reduction in Health Anxiety Inventory score' [130] and 'cost per additional successfully treated patient' [106], the cost-effectiveness of different treatments within UPS could not be compared.

Limitations

In the model, several assumptions were made, of which some might be considered as in favor of the cost-effectiveness of the group training, while others might be considered as conservative. For instance, assuming 'transition balance' in the waiting list condition might be considered as enhancing cost-effectiveness, as then 'spontaneous improvement' was balanced with deterioration. The idea of 'transition balance' was based on the fact that the nature of UPS of this patient group was chronic: the minimum duration of UPS was six months and its median duration was nine years. Furthermore, the effect of the 'transition balance' was limited by the time horizon of four years and by the finding that a satisfying incremental cost-effectiveness ratio was already reached after 18 months.

Merging the training groups 1 and 2 might have a favorable effect on cost-effectiveness. However, we tested the effect of this merging in a sensitivity analysis and did not find such a favorable effect.

The assumption that none or only a limited amount of productivity losses occurred as a result of attending the training might be considered as enhancing cost-effectiveness. However, the assumption was supported by the facts that most patients in our study group had only limited working obligations, and they could attend the training after working hours.

The assumption that there were no differences in terms of mortality might be considered as a conservative assumption. As the physical quality of life improved as a result of the training, the life expectancy might have been increased too.

The choice of a cut-off score of 40 on the physical component summary of the SF-36 and the use of constant costs and quality of life values for the health states over time might all have had an effect on the results, although it is unlikely that any other 'reasonable alternative cut-off score' would have shown very different results. From a clinical point of view, the use of change scores to define transitions in health states might be more appropriate than the use of a cut-off score, as change scores would reflect a similar amount of change at different quality-of-life levels. By this, change scores would most likely show more transitions in health states than a cut-off score at a fixed quality-of-life level would do. As this cut-off score was also fixed at a quality of life level within the general population's range, the cut-off score used might be seen as conservative.

Theoretical implications

The aim of the cognitive-behavioral group training is to improve health-related quality of life of patients with UPS. Because patients' quality of life is also negatively related to being older, being female, having a low level of education, living without a partner, having one or more comorbid medical conditions [145], and having one or more comorbid mental disorders [38; 99] and given the fact that patients with UPS seem to run a high risk on these conditions [14; 38; 56; 67; 68; 112; 165], only a modest increase in quality of life should be expected. This modest ambition is often accompanied by the claim that treatment will reduce healthcare consumption [80], which would be both beneficial for patients as it might avoid unnecessary medical interventions and perhaps even iatrogenesis and beneficial for society as it might reduce healthcare costs. There is hardly any data to support this claim, but the results of the present study indeed suggest that this hypothesis might be true: the increase of QALYs was modest, but the decrease of costs was substantial, which makes the treatment cost saving and preferable over the waiting list condition.

Clinical and policy implication

The clinical and policy implication of this study is that the favorable results of the cost-effectiveness analysis are an additional and strong argument to implement and reimburse cognitive-behavioral therapy for patients with UPS. Such an implementation will give

patients the opportunity to increase their quality of life and support healthcare services to provide the appropriate and most cost-effective treatment for this patient group. The results are also useful for the payers of healthcare services, as the results show strong evidence of cost saving after treatment.

Further research

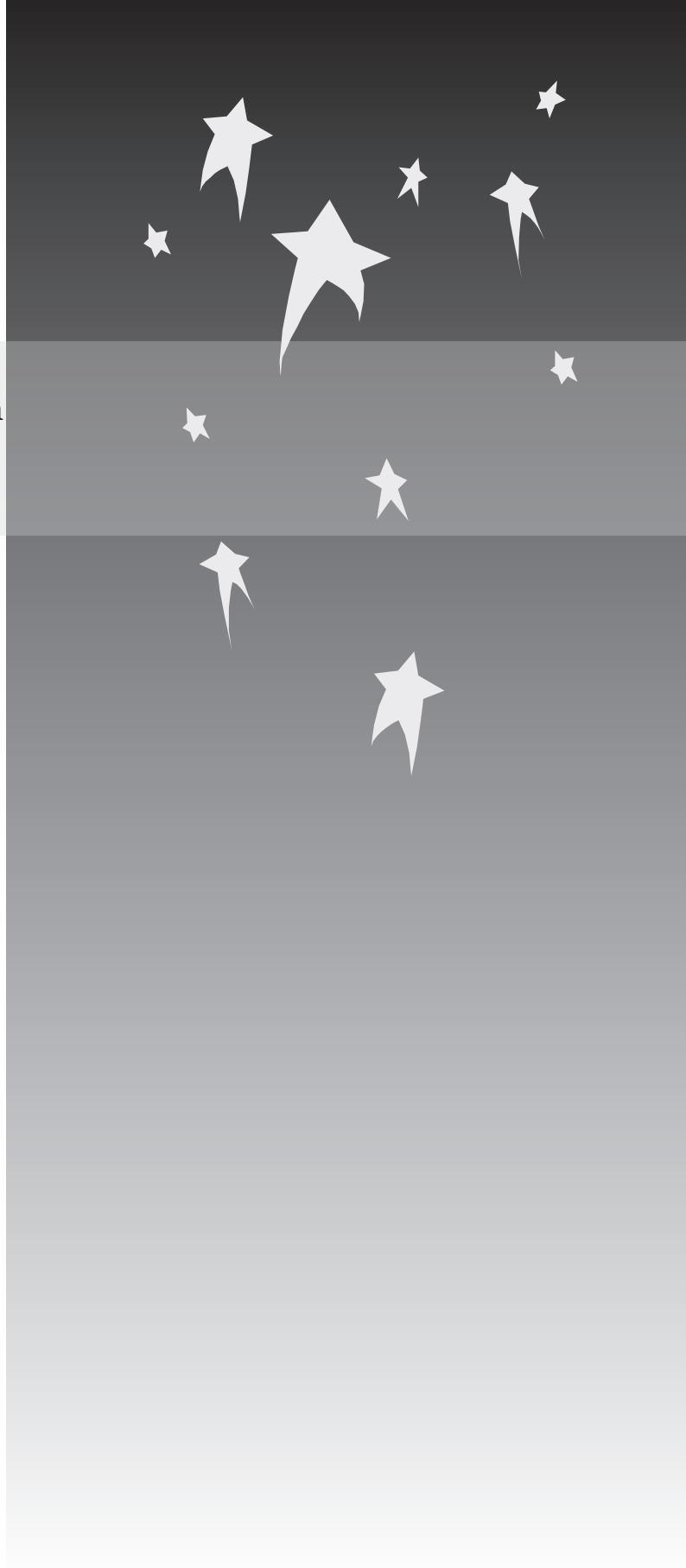
It is tempting to advice, that further research should be a randomized controlled trial with a longer follow-up in the control waiting list condition. In that way, we could test the assumption of 'transition balance' between health states in the waiting list condition. However, given that we have already established effectiveness of this treatment, it will be unlikely that such design will be approved by any medical ethical research committee. Instead, it might be more realistic to advise to conduct a cost-effectiveness study, in which different therapies for patients with UPS are compared head-to-head. Another advisable investigation might be 'implementation research', as it is likely that treatment compliance of both patients and healthcare providers will influence the cost-effectiveness of the treatment [71].

Conclusion

This study is one of the few cost-effectiveness studies in patients with UPS, and the first to use a state-of-the-art health economic model and the preferred outcome in health economics: QALYs. Results of this study show that the cognitive-behavioral group training is a cost-effective treatment in patient with UPS compared with a waiting list condition.

Chapter 9

General discussion



Introduction

Unexplained Physical Symptoms (UPS) are physical symptoms that cannot be fully explained by a known medical condition. In certain cases, these symptoms also fulfill the DSM-IV criteria of undifferentiated somatoform disorder or chronic pain disorder. UPS defined in these DSM-IV terms is a serious condition from patients' perspective and from societal perspective.

From patients' perspective, UPS is a burden as it is a persistent condition [11] which is associated with high comorbidity of DSM-IV Axis I disorders [14; 38; 99], Axis II disorders [37; 56; 57; 66; 76; 95; 100; 114; 127; 157], and somatic disorders [14; 165]. These symptoms influence physical, behavioral, affective, cognitive and social aspects of life [131]. Although these influences might not always have to be adverse, the persistency of UPS will mostly end in perpetuating vicious circles that maintain or aggravate UPS, which diminish patients' quality of life. Patients seek help for their UPS mainly in medical services [14; 87], where they leave empty-handed or worse, with feelings of not being taken seriously or being rejected [40; 42].

From societal perspective, UPS is a burden, as it is a highly prevalent condition [38], and patients with UPS use the scarce and expensive resources in medical care services more often than other patient groups [14; 135]. After the first consultations [85], the use of these resources does not seem to result in a favorable outcome anymore [3; 9; 105; 126; 153; 156]. Not only patients, but also physicians experience negative feelings, when asked for help by patients with UPS [128].

Cognitive-behavioral therapy does result in positive outcome in patients with UPS [86; 111; 152] without causing harmful effects [65]. As this therapy seems to be mainly effectively if it is conducted at specialized centers or mental health centers [4; 86; 122], and patients refuse to be referred to mental health centers [5; 122], this therapy reaches only a small group of patients.

The aims of the study on which this thesis is based were the following:

1. evaluating how quality of life of patients with UPS and societal costs associated with them relate to corresponding data in other patient groups;
2. developing a group training for patients with UPS tailored to their perspective and conducted by secondary community mental health services reaching out into primary care;
3. investigating its effectiveness and the preservation of this effect over a time period of one year;
4. examining whether diagnostics and assessment for this training are useful;
5. evaluating the cost-effectiveness of this training.

These aims resulted in the following research questions and hypotheses:

1.a) What is the quality of life of patients with UPS, and how does it relate to other patient groups?
The study's *hypothesis* was that patients with UPS will have a poor quality of life. Their quality of life was expected to be poorer than that of most other patient groups.

1.b) What are the healthcare-related costs associated with patients with UPS, and how do they relate to corresponding costs in other patient groups?
The study's *hypothesis* was that healthcare-related costs associated with UPS will be high due to high use of medical services. These costs associated with UPS were expected to be higher than those associated with other diseases.

1.c) What are the work-related costs associated with patients with UPS, and how do they relate to corresponding costs in other patient groups?
The study's *hypothesis* was that work-related costs associated with UPS will be high due to absenteeism (absence from work), presenteeism (reduced on-the-job productivity) and paid substitution of domestic tasks. These costs associated with UPS were expected to be higher than those associated with other diseases.

2. Is it possible to develop an easily accessible cognitive-behavioral group training for a large group of patients with UPS that is feasible for a secondary community mental health service reaching out into primary care?
The study's *hypothesis* was that it will be possible to develop an easily accessible cognitive-behavioral group training for a large group of patients with UPS that is feasible for a secondary community mental health service reaching out into primary care.

3.a) Can such a cognitive-behavioral group training effectively improve quality of life of patients with UPS?
The study's *hypothesis* was that the cognitive-behavioral group training will effectively improve patients' quality of life.

3.b) Is patients' improved quality of life preserved in a one-year follow-up period?
The study's *hypothesis* was that patients' improved quality of life will be preserved during the follow-up.

4. Do variables assessed at baseline and used in routine-practice assessments consistently predict the outcome of the cognitive-behavioral group training, after control for pretreatment scores on the outcome measure and for sociodemographic variables?
In line with clinical practice, the study's *hypothesis* was that better outcome will be predicted by the following: fewer psychological symptoms and personality-disorder characteristics, the absence of a psychiatric history, and a better quality of life in the mental domain.

5. Is the cognitive-behavioral group training cost-effective compared with a waiting list for patients with UPS?
   The study's *hypothesis* was that the ratio between costs and effects of the cognitive-behavioral group training will be favorable from a societal perspective using a cost-effectiveness ratio of €30,000 per QALY.

Main findings

The study gave the following answers to the research questions:

1.a) What is the quality of life of patients with UPS, and how does it relate to other patient groups?
   Patients with UPS reported poor quality of life in the physical and social domains, and relatively better quality of life in the mental domain. This profile seemed to resemble most closely to the one found in patients with physical diseases. The overall quality of life of patients with UPS was among the poorest compared with those of patients with mental disorders, and of patients with physical symptoms explained by a known medical condition.

1.b) What are the healthcare-related costs associated with patients with UPS, and how do they relate to corresponding costs in other patient groups?
   The mean healthcare-related costs associated with patients with UPS were estimated to be €3,122.93 per patient per year, representing an annual healthcare expenditure for UPS of more than three billion euros in the Netherlands. This was more than four percent of the total Dutch annual healthcare expenditures. Relative to the total spectrum of diseases, only costs for dementia and mental retardation were higher.

1.c) What are the work-related costs associated with patients with UPS, and how do they relate to corresponding costs in other patient groups?
   The mean total work-related costs associated with patients with UPS were estimated to be €3,692.98 per patient per year, representing an annual work-related expenditure for UPS of almost four billion euros in the Netherlands. These work-related costs were mainly caused by absenteeism. Absenteeism in patients with UPS was the highest of that in other patient groups. The mean cost of absenteeism was estimated to be €2,403.92 per patient per year. The rest of the work-related costs was caused by the cost of presenteeism with an estimated mean of €855.79 per patient per year, and of substitution of domestic tasks by paid professionals with an estimated mean of €433.27 per patient per year.

2. Is it possible to develop an easily accessible cognitive-behavioral group training for a large group of patients with UPS that is feasible for a secondary community mental health service reaching out into primary care?

The cognitive-behavioral group training was developed and it appeared to be feasible in primary medical care, conducted by secondary mental healthcare specialists. By doing so, the limited treatment capacity for UPS was increased. The expectation was that the training was indeed easily accessible because of the increased capacity, but also because of its tailoring to patients' perspective on symptoms and goals of treatment. Whether this expectation on easily accessibility was true, cannot be answered as this was not investigated in our study. However, a couple of experiences seem to suggest easily accessibility: the findings of two earlier studies showing the ineffectiveness of treatment based on the original (not-tailored) consequences model in general practice [9; 12], the high number of successful referrals, and, in general, the nice reactions of patients to the training.

3.a) Can such a cognitive-behavioral group training effectively improve quality of life of patients with UPS?

The training improved patients' quality of life in the physical domain, which was the domain patients reported as most burdensome at baseline. It did not influence quality of life in the mental domain, which was already relatively high at baseline.

3.b) Is patients' improved quality of life preserved in a one-year follow-up period?

The improvement in patients' quality of life in the physical domain remained stable over a year. It even slightly increased in the one-year follow-up period.

4. Do variables assessed at baseline and used in routine-practice assessments consistently predict the outcome of the cognitive-behavioral group training, after control for pretreatment scores on the outcome measure and for sociodemographic variables?

Only short-term outcome of the training, and not immediate and long-term outcome, could be predicted by variables used in routine-practice assessments. Better short-term outcome was predicted by– in descending order of strength 1.) a higher number of psychological symptoms at baseline, 2.) a better quality of life in the mental domain at baseline, 3.) a lower number of personality-disorder characteristics at baseline, and 4.) the presence of a psychiatric history at baseline. As this predictor set only explained 15% of the variance of short-term outcome and did not significantly predict outcome consistently over time, the need to use selection and allocation of patients with UPS for the training on basis of this predictor set would be doubtful. It seems that this selection would unnecessarily deprive patients of an effective treatment.

5. Is the cognitive-behavioral group training cost-effective compared with a waiting list for patients with UPS?

The costs and effects of the training had a favorable ratio. After a time horizon of 18 months, the cost-effectiveness was below the threshold of €30,000 per QALY.

Strengths and limitations

The study on which this thesis is based was conducted in the daily practice of a secondary community mental health service, Riagg Rijnmond. This institution sought close collaboration with primary and secondary medical care centers to inform physicians about the new treatment possibility for patients with UPS and to find locations for organizing the training. The study was financed within the reimbursement practice of that time. This framework of the study had its strengths and limitations.

Strengths are particularly found on the level of generalizability of the study. Conducting the training in the daily practice and financing it within the regular reimbursement practice increased the chance of developing an evidence-based program, which will be feasible in a daily practice and can be implemented without problems. Kathol et al. [75] showed the relevance of this kind generalizability, as most evidence-based programs integrating mental health services in primary care could not be successfully implemented after completion of the study due to the fact that research funds were not substituted within the current reimbursement practice.

Conducting the training in close collaborations with several primary and secondary medical care centers resulted in large diversity of referring physicians and, consequently, in a large diversity of patients ranging from patients with fulltime jobs to patients who were spending their time mostly in bed. This made our results more generalizable than most studies as they usually explored UPS either in general practice [3; 9; 18; 94; 105; 126; 153; 156] or medical subspecialty clinics or mental health centers [4; 86; 122].

Conducting the training in the daily practice meant using a liberal policy in regard to the inclusion of patients, as secondary community mental health services have patient care and not research as their primary task. Due to this liberal inclusion, the presence of comorbid DSM-IV Axis I disorders and/or DSM-IV Axis II disorders was only carefully listed without excluding patients with these comorbidities. This gave the opportunity to investigate the effect of the group training in a representative group seen in daily practice and, also, to explore the actual instead of the presumed influence of comorbidity on its effectiveness.

Also, due to the liberal inclusion, only a minimum duration of UPS was fixed according to the DSM-IV definition of UPS, but no maximum duration was set. This resulted in a study group with a median duration of UPS of nine years. Despite this long duration of UPS, the study still showed that the training was effective for the quality of life in the physical domain, which was reported as most burdensome by patients with UPS. As studies have shown that the prognosis of UPS becomes more unfavorable if the

duration of UPS is longer [72; 84; 85; 143], these findings on the effectiveness were more convincing.

Conducting the training in the daily practice also meant that six different psychologists with different experience levels gave the training at four different local medical settings. This suggested that the training was generalizable to different circumstances and different trainers. This generalizability was also possible, as the training is theory-based and elaborately described in a manual [170].

The limitations of doing a study in the daily practice were in particular associated with restricted resources. Restricted resources reduced the possibilities to check whether the contacts with patients went as preliminary planned. Contacts that would have been of value to check were those during the inclusion and those during training. To check the reliability of the contacts during the inclusion, an inter-rater-reliability could have been calculated for the *Structured Clinical Interview for DSM-IV Axis I Disorders/Patient edition* (SCID-I/P). The absence of this reliability was especially regrettable, as the number of UPS classified by SCID-I/P as undifferentiated somatoform disorder was lower than the number of UPS classified as chronic pain disorder – the opposite of what was found in a study in Dutch general practices [38]. To clarify this difference, the SCID-I/P interviews were more closely examined. This showed that, due to the interviewers' or patients' emphasis on pain in the presence of a broad spectrum of symptoms, syndromes such as fibromyalgia or chronic fatigue syndrome had sometimes been misclassified as chronic pain disorder. These misclassifications might have inflated the number of chronic pain disorders at the expense of undifferentiated somatoform disorder.

To check whether the contacts with patients during the group training went as preliminary planned, the group sessions could have been recorded and, afterwards, rated by independent raters to verify treatment integrity. Now, treatment integrity was only stimulated by supervision given by the developer of the manual (LZ) before each session of the training.

Also, the possibilities for the control condition in the study design were limited due to the priority given to patient care. Therefore, patients on the waiting list had to wait only 13 weeks for the group training – the same period as the training itself. This deprived the study of a control condition for the three-month follow-up and for the one-year follow-up. However, the time frame of these follow-up assessments was longer than the usual time frame of intervention studies for UPS that ranged from three to 12 months with a mean of six months [4].

Not only the absence of a prolonged control condition for the influence of time and other not-intervention-related circumstances, but also the absence of a control condition for the influence of intervention-related aspects was a limitation. Because of this limitation, the measured effects could not be attributed to the specific therapeutic interventions of the cognitive-behavioral group training. If a control intervention

group (e.g. relaxation, solely psycho-education, self help, individual treatment) had been included, it would have been possible to explore whether the training itself had supplementary effects in comparison to other interventions.

Clinical and policy implications

In the Netherlands, multidisciplinary guidelines are developed for mental healthcare services to stimulate the use of evidence-based diagnosis and treatment in mental disorders. For UPS, a multidisciplinary guideline called 'Multidisciplinary guidelines for the diagnosis and treatment of somatic insufficient explained physical symptoms and somatoform disorders' is available since 2011 [93]. This guideline should have described the full range of evidence-based diagnosis and treatment for unexplained physical symptoms ranging from a single, uncomplicated and non-persistent unexplained physical symptom up to and including multiple, complicated and persistent symptoms classified as somatoform disorders. However, the developers of this guideline reported that the bulk of research data appeared to be insufficient and too fragmented in some areas to be able to do so, and, in other areas, too rich to summarize it within the time span of the development of this guideline [93]. The former resulted in the omission of a description of evidence-based treatment for undifferentiated somatoform disorder and the latter in the omission of a summary of evidence-based treatments for chronic pain disorder. The study, on which this thesis is based, included exactly these two disorders and can fill in these gaps.

Despite missing data, the guideline suggests to organize the treatment for unexplained physical symptoms on the principles of stepped care of Henningsen et al. [68], in which the intensity of the offered treatment is adjusted to the severity of the symptoms and the expected prognosis. Step One is used in uncomplicated symptoms, for which the guideline suggests that the general practitioner should do a thorough medical examination, be attentive for psychosocial problems, give psycho-education and short-term cognitive-behavioral therapy. Step Two is used in moderately complicated symptoms with mental and/or physical comorbidity, for which the guideline suggests that the general practitioner, medical specialist or psychiatrist should be the case manager and comorbidity should be treated with medication and cognitive-behavioral therapy. Step Three is used in severe complicated symptoms classified as a somatoform disorder, for which the guideline suggests that a case manager should to limit iatrogenic artifacts, motivate patients for cognitive-behavioral therapy or, in patients with multiple severe symptoms, arrange hospitalization in a tertiary multidisciplinary hospital.

At the end of Step One, this guideline suggests short-term cognitive-behavioral therapy carried out by general practitioners. However, earlier studies have shown problems around cognitive-behavioral therapy carried out by general practitioners,

which included that it: 1) had an inconclusive effect [3; 9; 105; 126; 153; 156], 2) was not feasible for general practitioners because of, for example, the limited time available in patient-physician encounters [43], 3) was uncomfortable for general practitioners who feel psychological unskilled [128; 159], and 4) was uncomfortable for patients resulting in hesitations to disclose psychosocial issues to their general practitioners [120]. Moreover, the capacity of this therapy, in which only one patient a time is seen, is rather small in comparison to the high prevalence of unexplained physical symptoms. The easily accessible cognitive-behavioral group training described in this thesis can solve these problems by substituting the cognitive-behavioral therapy carried out by general practitioners in the stepped care from the end of Step One to the beginning of Step Three.

This substitution will result in a broader use of the group training than investigated, as its effectiveness was only investigated for unexplained physical symptoms which could be classified as undifferentiated somatoform disorder and chronic pain disorder. On the basis of these DSM-IV classifications, the training should be included only in Step Three of the stepped care. However, no profits are gained by withholding an effective treatment from patients with less severe symptoms, because unexplained physical symptoms seem to persist if these symptoms do not recover or improve within a few weeks after thorough medical examination [85]. So, these symptoms will eventually meet these classifications, and withholding an effective treatment for a longer period will lead to more unfavorable and unnecessary consequences for both patients and society. The cost-effectiveness study of this thesis suggested that the training is a worthwhile investment from societal perspective to raise the health of a large group of patients. This is due to the favorable combination of the effects, the low cost of the treatment and the savings which are established in the healthcare services and in improved productivity of patients. The favorable results of the cost-effectiveness analysis are an additional and strong argument to implement and reimburse cognitive-behavioural therapy for UPS. Such an implementation will give patients the opportunity to increase their quality of life and support healthcare services to provide the appropriate and most cost- effective treatment for this patient group. The results are also useful for the payers of healthcare services, as the results showed strong evidence of cost saving after treatment.

A successful implementation of the group training in this stepped care asks for a sufficient reimbursement practice of the healthcare system. However, from January 2012, the Ministry of Health, Welfare and Sport (VWS) has changed this practice by introducing a mandatory contribution for mental health services to reduce the growth of healthcare expenditures. By this, patients have to pay €200 for the training conducted by secondary community mental health service, while diagnosis and treatment in a general practice are still totally covered by the health insurance. It is to be expected that this will decrease the accessibility of the training and will increase the use of medical services. In contrast to the aim of the Ministry of Health, Welfare and Sport (VWS), this might

expand instead of reduce growth of healthcare expenditures. However, the last words about the mandatory contribution for mental health services have not been said, as the budgetary proposal for 2013 (Spring Agreement) between different political parties has shown.

Future research

Clinical practice and research in patients with UPS are seriously complicated by the absence of a shared definition. This absence makes the communication about these symptoms between patients, clinicians and researchers within and between disciplines difficult. To overcome this, the new definition 'Somatic Insufficient Explained Physical Symptoms' (SOLK) was introduced in the Netherlands within the framework of the Dutch guideline for diagnosis and treatment of patients with UPS. However, the use of this term is not advisable, because it resembles too closely to the term 'medically unexplained', by which at least one third of the patients with UPS is offended [151]. Also, there is no internationally comparable term for 'Somatic Insufficient Explained Physical Symptoms' that can be used in the communication with clinicians and researchers outside the Netherlands. The Statistical Manual for Mental Disorders (DSM) aims to develop a common language between all stakeholders. In the fifth revision [8], the term 'Somatic Symptom Disorder' is proposed, which is defined as distressing and/or disabling somatic symptoms in combination with excessive thoughts, feelings, and behaviors in response to these somatic symptoms, which typically persist for more than six months. Its severity is expressed in the number of symptoms and disabilities. Future research should use this term and specifiers to promote transparency in the communication to patients, clinicians and researchers and to increase generalizability of research findings.

Using this DSM-V definition and specifiers of UPS, future research in the Netherlands might investigate to which degree the group training described in this thesis and the stepped care described in the Dutch guideline for UPS are feasible on a large scale, as a large-scale implementation is necessary in view of the high prevalence of UPS. This feasibility study should not only include the technical feasibility but also the interest and enthusiasm of mental health professionals and general practitioners to be trained in the different interventions and to implement these interventions in their own settings. Moreover, the adherence of the mental health professionals and general practitioners to the intervention protocol should be investigated. Subsequently, the difference in clinical effectiveness of these interventions might be assessed in a randomized controlled trial on a national scale. The different conditions of this trial should at least include both interventions and care-as-usual. Other important variables which might be considered as experimental conditions are patient's preference for a specific kind of intervention and healthcare provider's preference for conducting a specific kind of intervention. Primary

outcome measures should match patients' goals for treatment, which are support from the healthcare provider [31,33], followed by improving daily functioning, and coping with UPS [33]. Last but not least, the cost-effectiveness of all interventions should be investigated in the same national randomized controlled trial. Instead of estimating the costs of healthcare expenditures using self-report questionnaires, the actually costs reimbursed by health insurance companies should be used as they lead to more objective data on cost-effectiveness. These reimbursed costs should be monitored for at least two years.

Finally

UPS is a burden for patients as well as for society. An easily accessible cognitive-behavioral group training tailored to patients' perspective can lessen this burden, as the training seems to have favorable results for patients during at least a year and is cost-effective after 18 months. This training does not require assessment and selection of patients, but its implementation does require a good collaboration between medical and mental services. Hopefully, this thesis will inspire these services to seek collaboration on small and large scale, and will stimulate policymakers and politicians to support this.

Appendices

Appendix A. Total number of patients with UPS and their annual healthcare expenditures

Sub-group	Percentage or number	Estimator
Prevalence of undifferentiated somatoform disorder in general practices [38]	*13.0%*	
Prevalence of chronic pain disorder in general practices [38]	*1.6%*	
Prevalence of Unexplained Physical Symptoms (UPS) in general practices		14.6%
Percentage of the general population visiting a general practice in 2007 [146]	72.4%	72.4%
Number of people in the general population aged between 20 and 40 years in 2007 [148]	*4,319,136*	
Number of people in the general population aged between 40 and 65 years in 2007 [148]	*5,713,401*	
Total number of people in the general population aged between 20 and 65 years		10,032,537
Total number of patients with Unexplained Physical Symptoms (UPS)		**1,060,479**
Mean medical costs per patient with Unexplained Physical Symptoms (UPS) per year [Chapter 2]		€3,122.93
Total annual healthcare expenditures related to Unexplained Physical Symptoms (UPS)		**€3,311,800,000**
Total Dutch annual healthcare expenditures [133]	€74,447,000,000	
The percentage of total annual healthcare expenditures related to UPS		**4.4%**

Appendix B. CONSORT checklist

Section/Topic	Item No	Checklist item	Reported in Chapter 6 section
Title and abstract			
	1a	Identification as a randomized trial in the title	Title
	1b	Structured summary of trial design, methods, results, and conclusions	Abstract
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	Introduction
	2b	Specific objectives or hypotheses	Objectives (Introduction)
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Study design (Methods)
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	Participants (Methods)
	4b	Settings and locations where the data were collected	Recruitment (Results)
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Interventions (Methods) Recruitment (Results) Intervention data (Results)
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	Outcomes (Methods) Recruitment (Results) Study design (Methods)
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	Sample size (Methods)
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomization:			
-sequence-generation	8a	Method used to generate the random allocation sequence	Randomization sequences generation (Methods)
	8b	Type of randomization; details of any restriction (such as blocking and block size)	Randomization sequences generation (Methods)
-allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Randomization allocation concealment (Methods)
-implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Randomization implementation (Methods)
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	Blinding (Methods)
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	Statistical methods (Methods)
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	N/A

Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	Figure 6.2 (Results)
	13b	For each group, losses and exclusions after randomization, together with reasons	Figure 6.2 (Results)
Recruitment	14a	Dates defining the periods of recruitment and follow-up	Recruitment (Results)
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 6.2 and 6.3 (Results)
Numbers analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Figure 6.2 (Results)
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Table 6.4 and 6.5 (Results)
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Ancillary analyses (Results)
Harms	19	All important harms or unintended effects in each group	Adverse events (Results)
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	Limitations (Discussion)
Generalizability	21	Generalizability (external validity, applicability) of the trial findings	Generalizability (Discussion)
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	Discussion
Other information			
Registration	23	Registration number and name of trial registry	Registration (Abstract) Ethics (Methods)
Protocol	24	Where the full trial protocol can be accessed, if available	Methods Ethics (Methods)
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	N/A

References

References

[1] Aaronson NK, Muller M, Cohen PDA, Essink-Bot M, Fekkes M, Sanderman R, Sprangers MAG, Te Velde AM, Verrips E. Translation, validation and norming of the Dutch language version of the SF-36 health survey in community and chronic disease populations. J Clin Epidemiol 1998;51(11):1055-1068.

[2] Aberson CL. Applied power analysis for the behavioral sciences. New York: Routledge, 2010.

[3] Aiarzaguena JM, Grandes G, Gaminde I, Salazar A, Sánchez Á, Ariño J. A randomized controlled clinical trial of a psychosocial and communication intervention carried out by GPs for patients with medically unexplained symptoms. Psychol Med 2007;37(2):283-294.

[4] Allen LA, Escobar JI, Lehrer PM, Gara MA, Woolfolk RL. Psychosocial treatments for multiple unexplained physical symptoms: a review of the literature. Psychosom Med 2002;64(6):939-950.

[5] Allen LA, Woolfolk RL. Cognitive behavioral therapy for somatoform disorders. Psychiatr Clin North Am 2010;33(3):579-593.

[6] Allen LA, Woolfolk RL, Escobar JI, Gara MA, Hamer RM. Cognitive-behavioral therapy for somatization disorder: a randomized controlled trial. Arch Intern Med 2006;166(14):1512-1518.

[7] APA. Beknopte handleiding bij de diagnostische criteria van de DSM-IV-TR. Lisse: Harcourt Assessment BV, 2005.

[8] APA. DSM-5 Web site. http://www.dsm5.org/ProposedRevision/Pages/proposedrevision.aspx?rid= 368#: American Psychiatric Association, 2012.

[9] Arnold IA, De Waal MWM, Eekhof JAH, Assendelft WJJ, Spinhoven P, Van Hemert AM. Medically unexplained physical symptoms in primary care: a controlled study on the effectiveness of cognitive-behavioral treatment by the family physician. Psychosomatics 2009;50(5):515-524.

[10] Arnold IA, De Waal MWM, Eekhof JAH, Spinhoven P, Assendelft WJJ, Van Hemert AM. Onverklaarde lichamelijke klachten en de samenhang met depressie en angst. Huisarts & Wetenschap 2007;50(13):686-689.

[11] Arnold IA, De Waal MWM, Eekhof JAH, Van Hemert AM. Somatoform disorder in primary care: course and the need for cognitive-behavioral treatment. Psychosomatics 2006;47(6):498-503.

[12] Arnold IA, Speckens AEM, Van Hemert AM. Medically unexplained physical symptoms: the feasibility of group cognitive-behavioural therapy in primary care. J Psychosom Res 2004;57(6):517-520.

[13] Arrindell WA, Ettema JHM. SCL-90/symptom checklist: handleiding bij een multidimensionele psychopathologie-indicator. Lisse: Swets Test Publishers, 2003.

[14] Barsky AJ, Orav EJ, Bates DW. Somatization increases medical utilization and costs independent of psychiatric and medical comorbidity. Arch Gen Psychiatry 2005;62(8):903-910.

[15] Barsky AJ, Orav EJ, Bates DW. Distinctive patterns of medical care utilization in patients who somatize. Med Care 2006;44(9):803-811.

[16] Blanchard EB, Lackner JM, Gusmano R, Gudleski GD, Sanders K, Keefer L, Krasner S. Prediction of treatment outcome among patients with irritable bowel syndrome treated with group cognitive therapy. Behav Res Ther 2006;44(3):317-337.

[17] Blankenstein AH. Somatising patients in general practice: reattribution, a promising approach. Amsterdam: Vrije Universiteit Amsterdam, 2001.

[18] Blankenstein AH, Van der Horst HE, Schilte AF, De Vries D, Zaat JOM, Knottnerus JA, Van Eijk JTM, De Haan M. Development and feasibility of a modified reattribution model for somatising patients, applied by their own general practitioners. Patient Educ Couns 2002;47(3):229-235.

[19] Bleichhardt G, Timmer B, Rief W. Prädiktoren für den direkten und längerfristigen therapieerfolg bei patienten mit somatoformen störungen nach verhaltenstherapeutischer behandlung. Zeitschrift für klinische psychologie, psychiatrie und psychotherapie 2005;53(1):40-58.

[20] Bonner D, Ron M, Chalder T, Butler S, Wessely S. Chronic fatigue syndrome: a follow up study. J Neurol Neurosurg Psychiatry 1994;57(5):617-621.

[21] Bornstein RF, Gold SH. Comorbidity of personality disorders and somatization disorder: a meta-analytic review. Journal of Psychopathology and Behavioral Assessment 2008;30(2):154-161.

[22] Bouman TK, Vervaeke GAC, Visser S. Behandelprotocol bij hypochondrie: therapeutenboek. Utrecht: Cure & Care Publishers, 2001.

[23] Bouwmans C, De Jong K, Timman R, Hakkaart- van Roijen L. Feasibility and validity of the TiC-P. Value in Health 2011;14(7):A426-A426.

[24] Braakman-Jansen LMA, Taal E, Kuper IH, Van de Laar MAFJ. Productivity loss due to absenteeism and presenteeism by different instruments in patients with RA and subjects without RA. Rheumatology (Oxford) 2012;51(2):354-361.

[25] Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. J Health Econ 2002;21(2):271-292.

[26] Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. Journal of health economics 2002;21(2):271-292.

[27] Brazier J, Roberts J, Tsuchiya A, Busschbach J. A comparison of the EQ-5D and SF-6D across seven patient groups. Health Econ 2004;13(9):873-884.

[28] Briggs A, Sculpher M, Claxton K. Decision modelling for health economic evaluation. Oxford: Oxford University Press, 2006.

[29] Brouwer WBF, Koopmanschap MA, Rutten FFH. Productivity losses without absence: measurement validation and empirical evidence. Health Policy 1999;48(1):13-27.

[30] Burton C, Weller D, Sharpe M. Functional somatic symptoms and psychological states: an electronic diary study. Psychosom Med 2009;71(1):77-83.

[31] Busschbach JJV, McDonnell J, Essink-Bot M-L, Van Hout BA. Estimating parametric relationships between health description and health valuation with an application to the EuroQol EQ-5D. J Health Econ 1999;18(5):551-571.

[32] Butterhoff JJF, Van Opdorp FAC. Geneesmiddeleninformatie. Maarssen: Elsevier gezondheidszorg, 2008.

[33] Buwalda FM, Bouman TK. Predicting the effect of psychoeducational group treatment for hypochondriasis. Clinical Psychology and Psychotherapy 2008;15(6):396-403.

[34] Cohen J. Statistical power analysis for the behavioral sciences. Hillsdale, New Jersey: Lawrence Erlbaum, 1988.

[35] Cohen J. A power primer. Psychol Bull 1992;112(1):155-159.

[36] Cunningham PJ. Beyond parity: primary care physicians' perspectives on access to mental health care. Health Aff (Millwood) 2009;28(3):w490-w501.

[37] Dammen T, Ekeberg Ø, Arnesen H, Friis S. Personality profiles in patients referred for chest pain: investigation with emphasis on panic disorder patients. Psychosomatics 2000;41(3):269-276.

[38] De Waal MWM, Arnold IA, Eekhof JAH, Van Hemert AM. Somatoform disorders in general practice: prevalence, functional impairment and comorbidity with anxiety and depressive disorders. Br J Psychiatry 2004;184(6):470-476.

[39] Deale A, Chalder T, Marks I, Wessely S. Cognitive behavior therapy for chronic fatigue syndrome: a randomized controlled trial. Am J Psychiatry 1997;154(3):408-414.

[40] Deale A, Wessely S. Patients' perceptions of medical care in chronic fatigue syndrome. Soc Sci Med 2001;52(12):1859-1864.

[41] Diekstra R. Ik kan denken/voelen wat ik wil. Lisse: Swets & Zeitlinger, 1999.

[42] Dirkzwager AJE, Verhaak PFM. Patients with persistent medically unexplained symptoms in general practice: characteristics and quality of care. BMC Family Practice 2007;8:33.

[43] Dowrick C, Gask L, Hughes JG, Charles-Jones H, Hogg JA, Peters S, Salmon P, Rogers AR, Morriss RK. General practitioners' views on reattribution for patients with medically unexplained symptoms: a questionnaire and qualitative study. BMC Family Practice 2008;9:46.

[44] Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. Methods for the economic evaluation of health care programmes. Oxford, England: Oxford University Press, 2005.

[45] Duddu V, Husain N, Dickens C. Medically unexplained presentations and quality of life: a study of a predominantly South Asian primary care population in England. J Psychosom Res 2008;65(4):311-317.

[46] Duijsens IJ, Haringsma R, Eurelings-Bontekoe EHM. V.K.P. handleiding. Leiderdorp: Datec, 2002.

[47] Dwamena FC, Lyles JS, Frankel RM, Smith RC. In their own words: qualitative study of high-utilising primary care patients with medically unexplained symptoms. BMC Family Practice 2009;10:67.

[48] Escobar JI, Gara MA, Diaz-Martinez AM, Interian A, Warman M, Allen LA, Woolfolk RL, Jahn E, Rodgers D. Effectiveness of a time-limited cognitive behavior therapy–type intervention among primary care patients with medically unexplained symptoms. Annals of family medicine 2007;5(4):328-335.

[49] Escobar JI, Waitzkin H, Silver RC, Gara M, Holman A. Abridged somatization: a study in primary care. Psychosom Med 1998;60(4):466-472.

[50] Evans CJ. Health and work productivity assessment: state of the art or state of flux? J Occup Environ Med 2004;46(6):S3-S11.

[51] Fenwick E, O'Brien BJ, Briggs A. Cost-effectiveness acceptability curves-facts, fallacies and frequently asked questions. Health Econ 2004;13(5):405-415.

[52] Fernández A, Saameño JAB, Pinto-Meza A, Luciano JV, Autonell J, Palao D, Salvador-Carulla L, Campayo JG, Haro JM, Serrano A, and the DASMAP investigators. Burden of chronic physical conditions and mental disorders in primary care. Br J Psychiatry 2010;196(4):302-309.

[53] Field A. Regression. Discovering statistics using SPSS. London: Sage, 2009. pp. 197-263.

[54] Fink P, Rosendal M. Recent developments in the understanding and management of functional somatic symptoms in primary care. Current Opinion in Psychiatry 2008;21(2):182-188.

[55] First MB, Spitzer RL, Gibbon M, Williams JBW. Structured clinical interview for DSM-IV axis I disorders. Amsterdam: Harcourt Test Publishers, 1999.

[56] Garcia-Campayo J, Alda M, Sobradiel N, Olivan B, Pascual A. Personality disorders in somatization disorder patients: a controlled study in Spain. J Psychosom Res 2007;62(6):675-680.

[57] Garyfallos G, Adamopoulou A, Karastergiou A, Voikli M, Ikonomidis N, Donias S, Giouzepas J, Dimitriou E. Somatoform disorders: comorbidity with other DSM-III-R psychiatric diagnoses in Greece. Compr Psychiatry 1999;40(4):299-307.

[58] Grandes G, Montoya I, Arietaleanizbeaskoa MS, Arce V, Sanchez A. The burden of mental disorders in primary care. European Psychiatry 2011;26(7):428-435.

[59] Green SB. How many subjects does it take to do a regression-analysis. Multivariate behavioral research 1991;26(3):499-510.

[60] Greeven A, Van Balkom AJ, Van der Leeden R, Merkelbach JW, Van den Heuvel OA, Spinhoven P. Cognitive behavioral therapy versus paroxetine in the treatment of hypochondriasis: an 18-month naturalistic follow-up. J Behav Ther Exp Psychiatry 2009;40(3):487-496.

[61] Hakkaart-van Roijen L, Tan SS, Bouwmans CAM. Handleiding voor kostenonderzoek, methoden en standaard kostprijzen voor economische evaluaties in de gezondheidszorg. Diemen: College voor Zorgverzekeringen, 2010.

[62] Hakkaart-van Roijen L. Handleiding Trimbos/iMTA questionnaire for Costs associated with Psychiatric Illness (TiC-P). Rotterdam: Institute for Medical Technology Assessment & Erasmus Universitair Medisch Centrum Rotterdam, 2002.

[63] Hakkaart-van Roijen L, Hoeijenbos MB, Regeer EJ, Ten Have M, Nolen WA, Veraart CPWM, Rutten FFH. The societal costs and quality of life of patients suffering from bipolar disorder in the Netherlands. Acta Psychiatr Scand 2004;110(5):383-392.

[64] Halm EA, Lee C, Chassin MR. Is volume related to outcome in health care? A systematic review and methodologic critique of the literature. Ann Intern Med 2002;137(6):511-520.

[65] Heins MJ, Knoop H, Prins JB, Stulemeijer M, Van der Meer JWM, Bleijenberg G. Possible detrimental effects of cognitive behaviour therapy for chronic fatique syndrome. Psychother Psychosom 2010;79(4):249-256.

[66] Henderson M, Tannock C. Objective assessment of personality disorder in chronic fatigue syndrome. J Psychosom Res 2004;56(2):251-254.

[67] Henningsen P, Zimmermann T, Sattel H. Medically unexplained physical symptoms, anxiety, and depression: a meta-analytic review. Psychosom Med 2003;65(4):528-533.

[68] Henningsen P, Zipfel S, Herzog W. Management of functional somatic syndromes. Lancet 2007;369(9565):946-955.

[69] Hiller W, Leibbrand R, Rief W, Fichter MM. Predictors of course and outcome in hypochondriasis after cognitive-behavioural treatment. Psychother Psychosom 2002;71(6):318-325.

[70] Hoogduin CAL, Hagenaars MA, Van Minnen A, Keijsers GPJ. Protocollaire behandeling van patiënten met ongewenste gewoonten: zelfcontroleprocedures. In: GPJ Keijsers, A Van Minnen, CAL Hoogduin, editors. Protocollaire behandelingen in de ambulante geestelijke gezondheidszorg 2. Houten/Diegem: Bohn Stafleu Van Loghum, 1999. pp. 237-252.

[71] Hutsebaut J, Bales DL, Busschbach JJV, Verheul R. The implementation of mentalization-based treatment for adolescents: a case study from an organizational, team and therapist perspective. International Journal of Mental Health Systems 2012;6(1):10.

[72] Jackson JL, Passamonti M. The outcomes among patients presenting in primary care with a physical symptom at 5 years. J Gen Intern Med 2005;20(11):1032-1037.

[73] Jaeschke R, Singer J, Guyatt GH. Measurement of health status: ascertaining the minimal clinically important difference. Control Clin Trials 1989;10(4):407-415.

[74] Jehoel-Gijsbers G. Beperkt aan het werk: rapportage ziekteverzuim, arbeidsongeschiktheid en arbeidsparticipatie. Den Haag: Sociaal en Cultureel Planbureau, 2010.

[75] Kathol RG, Butler M, McAlpine DD, Kane RL. Barriers to physical and mental condition integrated service delivery. Psychosom Med 2010;72(6):511-518.

[76] Katon WJ, Ries RK, Kleinman A. Part II: a prospective DSM-III study of 100 consecutive somatization patients. Compr Psychiatry 1984;25(3):305-314.

[77] Kellner R. Prognosis of treated hypochondriasis: a clinical study. Acta Psychiatr Scand 1983;67(2):69-79.

[78] Klein Hesselink J, Hooftman W, Koppes L. Ziekteverzuim in Nederland in 2010. Hoofddorp: TNO, 2012.

[79] Koch H, Van Bokhoven MA, Ter Riet G, Van der Weijden T, Dinant GJ, Bindels PJE. Demographic characteristics and quality of life of patients with unexplained complaints: a descriptive study in general practice. Qual Life Res 2007;16(9):1483-1489.

[80] Konnopka A, Schaefert R, Heinrich S, Kaufmann C, Luppa M, Herzog W, König HH. Economics of medically unexplained symptoms: a systematic review of the literature. Psychother Psychosom 2012;81(5):265-275.

[81] Kontodimopoulos N, Aletras VH, Paliouras D, Niakas D. Mapping the cancer-specific EORTC QLQ-C30 to the preference-based EQ-5D, SF-6D, and 15D instruments. Value in Health 2009;12(8):1151-1157.

[82] Kontodimopoulos N, Pappa E, Papadopoulos AA, Tountas Y, Niakas D. Comparing SF-6D and EQ-5D utilities across groups differing in health status. Qual Life Res 2009;18(1):87-97.

[83] Kooiman CG, Bolk JH, Brand R, Trijsburg RW, Rooijmans HG. Is alexithymia a risk factor for unexplained physical symptoms in general medical outpatients? Psychosom Med 2000;62(6):768-778.

[84] Kooiman CG, Bolk JH, Rooijmans HGM, Trijsburg RW. Alexithymia does not predict the persistence of medically unexplained physical symptoms. Psychosom Med 2004;66(2):224-232.

[85] Kroenke K. Patients presenting with somatic complaints: epidemiology, psychiatric co-morbidity and management. International Journal of Methods in Psychiatric Research 2003;12(1):34-43.

[86] Kroenke K. Efficacy of treatment for somatoform disorders: a review of randomized controlled trials. Psychosom Med 2007;69(9):881-888.

[87] Kroenke K, Sharpe M, Sykes R. Revising the classification of somatoform disorders: key questions and preliminary recommendations. Psychosomatics: Journal of Consultation Liaison Psychiatry 2007;48(4):277-285.

[88] Kroenke K, Swindle R. Cognitive-behavioral therapy for somatization and symptom syndromes: a critical review of controlled clinical trials. Psychother Psychosom 2000;69(4):205-215.

[89] Kruijshaar ME, Hoeymans N, Bijl RV, Spijker J, Essink-Bot ML. Levels of disability in major depression: findings from the Netherlands mental health survey and incidence study (NEMESIS). J Affect Disord 2003;77(1):53-64.

[90] Lacy NL, Paulman A, Reuter MD, Lovejoy B. Why we don't come: patient perceptions on no-shows. Annals of family medicine 2004;2(6):541-545.

[91] Lambert MJ. Early response in psychotherapy: further evidence for the importance of common factors rather than «placebo effects». J Clin Psychol 2005;61(7):855-869.

[92] Lambert MJ, Barley DE. Research summary on the therapeutic relationship and psychotherapy outcome. Psychotherapy: theory, research, practice training 2001;38(4):357-361.

[93] Landelijke Stuurgroep Multidisciplinaire Richtlijnontwikkeling in de GGZ. Multidisciplinaire richtlijn: somatisch onvoldoende verklaarde lichamelijke klachten en somatoforme stoornissen. Utrecht: Trimbos-instituut, 2010.

[94] Larisch A, Schweickhardt A, Wirsching M, Fritzsche K. Psychosocial interventions for somatizing patients by the general practitioner: a randomized controlled trial. J Psychosom Res 2004;57(6):507-514.

[95] Leibbrand R, Hiller W, Fichter MM. Effect of comorbid anxiety, depressive, and personality disorders on treatment outcome of somatoform disorders. Compr Psychiatry 1999;40(3):203-209.

[96] Leibbrand R, Hiller W, Fichter MM. Influence of personality disorders on therapy outcome in somatoform disorders at 2-year follow-up. The Journal of Nervous and Mental Disease 1999;187(8):509-512.

[97] Longmore RJ, Worrell M. Do we need to challenge thoughts in cognitive behavior therapy? Clin Psychol Rev 2007;27(2):173-187.

[98] Looper KJ, Kirmayer LJ. Behavioral medicine approaches to somatoform disorders. J Consult Clin Psychol 2002;70(3):810-827.

[99] Löwe B, Spitzer RL, Williams JBW, Mussell M, Schellberg D, Kroenke K. Depression, anxiety and somatization in primary care: syndrome overlap and functional impairment. Gen Hosp Psychiatry 2008;30(3):191-199.

[100] Maina G, Albert U, Gandolfo S, Vitalucci A, Bogetto F. Personality disorders in patients with burning mouth syndrome. J Personal Disord 2005;19(1):84-93.

[101] Michaelson P, Sjölander P, Johansson H. Factors predicting pain reduction in chronic back and neck pain after multimodal treatment. Clin J Pain 2004;20(6):447-454.

[102] Miles JNV, Shevlin M. Issues in regression analysis. Applying regression and correlation: a guide for students and researchers. London: Sage, 2001. pp. 119-121.

[103] Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, Elbourne D, Egger M, Altman DG. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. Br Med J 2010;340:c869.

[104] Moock J, Kohlmann T. Comparing preference-based quality-of-life measures: results from rehabilitation patients with musculoskeletal, cardiovascular, or psychosomatic disorders. Qual Life Res 2008;17(3):485-495.

[105] Morriss R, Dowrick C, Salmon P, Peters S, Dunn G, Rogers A, Lewis B, Charles-Jones H, Hogg J, Clifford R, Rigby C, Gask L. Cluster randomised controlled trial of training practices in reattribution for medically unexplained symptoms. Br J Psychiatry 2007;191(6):536-542.

[106] Morriss R, Gask L, Ronalds C, Downes-Grainger E, Thompson H, Leese B, Goldberg D. Cost-effectiveness of a new treatment for somatized mental disorder taught to GPs. Fam Pract 1998;15(2):119-125.

[107] Nakao M, Fricchione G, Myers P, Zuttermeister PC, Baim M, Mandle CL, Medich C, Wells-Federman CL, Arcari PM, Ennis M, Barsky AJ, Benson H. Anxiety is a good indicator for somatic symptom reduction through behavioral medicine intervention in a mind/body medicine clinic. Psychother Psychosom 2001;70(1):50-57.

[108] Nater UM, Jones JF, Lin JMS, Maloney E, Reeves WC, Heim C. Personality features and personality disorders in chronic fatigue syndrome: a population-based study. Psychother Psychosom 2010;79(5):312-318.

[109] Nelson-Jones R. The theory and practice of counselling psychology. London: Cassell Educational Limited, 1982. pp. 250-257.

[110] Nezu AM, Nezu CM, Friedman SH, Faddis S, Houts PS. Helping cancer patients cope: a problem-solving approach. Washington, DC, US: American Psychological Association, 1998.

[111] Nezu AM, Nezu CM, Lombardo ER. Cognitive-behavior therapy for medically unexplained symptoms: a critical review of the treatment literature. Behavior Therapy 2001;32(3):537-583.

[112] Nimnuan C, Hotopf M, Wessely S. Medically unexplained symptoms: an epidemiological study in seven specialities. J Psychosom Res 2001;51(1):361-367.

[113] Nordin TA, Hartz AJ, Noyes R, Anderson MC, Rosenbaum ME, James PA, Ely JW, Agarwal N, Levy BT. Empirically identified goals for the management of unexplained symptoms. Fam Med 2006;38(7):476-482.

[114] Noyes R, Langbehn DR, Happel RL, Stout LR, Muller BA, Longley SL. Personality dysfunction among somatizing patients. Psychosomatics 2001;42(4):320-329.

[115] Oostburg RIM. Relaxatietraining voor de uitvoeringspraktijk: verbatim protocol (ten behoeve van hulpverleners). 1997.

[116] Osoba D. Interpreting the meaningfulness of changes in health-related quality of life scores: lessons from studies in adults. Int J Cancer 1999;83(S12):132-137.

[117] Pallant J. SPSS survival manual: a step by step guide to data analysis using SPSS for Windows (Version 12). Maidenhead Berkshire: Open University Press, 2005.

[118] Paterson C, Taylor RS, Griffiths P, Britten N, Rugg S, Bridges J, McCallum B, Kite G. Acupuncture for 'frequent attenders' with medically unexplained symptoms: a randomised controlled trial (CACTUS study). Br J Gen Pract 2011;61(587):e295-e305.

[119] Peeters FPML, Bayer H. ‹No show› for initial screening at a community mental health centre: rate, reasons and further help-seeking. Soc Psychiatry Psychiatr Epidemiol 1999;34(6):323-327.

[120] Peters S, Rogers A, Salmon P, Gask L, Dowrick C, Towey M, Clifford R, Morriss R. What do patients choose to tell their doctors? Qualitative analysis of potential barriers to reattributing medically unexplained symptoms. J Gen Intern Med 2008;24(4):443-449.

[121] Prins J, Bleijenberg G, Rouweler EK, Van der Meer J. Effect of psychiatric disorders on outcome of cognitive-behavioural therapy for chronic fatigue syndrome. The British Journal of Psychiatry 2005;187(2):184-185.

[122] Raine R, Haines A, Sensky T, Hutchings A, Larkin K, Black N. Systematic review of mental health interventions for patients with common somatic symptoms: can research evidence from secondary care be extrapolated to primary care? Br Med J 2002;325(7372):1082-1092.

[123] Reid S, Wessely S, Crayford T, Hotopf M. Medically unexplained symptoms in frequent attenders of secondary health care: retrospective cohort study. Br Med J 2001;322(7289):767.

[124] Reynolds KJ, Vernon SD, Bouchery E, Reeves WC. The economic impact of chronic fatigue syndrome. Cost Effectiveness and Resource Allocation 2004;2(1):4.

[125] Rief W, Hiller W, Geissner E, Fichter MM. A two-year follow-up study of patients with somatoform disorders. Psychosomatics 1995;36(4):376-386.

[126] Rosendal M, Olesen F, Fink P, Toft T, Sokolowski I, Bro F. A randomized controlled trial of brief training in the assessment and treatment of somatization in primary care: effects on patient outcome. Gen Hosp Psychiatry 2007;29(4):364-373.

[127] Rost KM, Akins RN, Brown FW, Smith GR. The comorbidity of DSM-III-R personality disorders in somatization disorder. Gen Hosp Psychiatry 1992;14(5):322-326.

[128] Salmon P, Peters S, Clifford R, Iredale W, Gask L, Rogers A, Dowrick C, Hughes J, Morriss R. Why do general practitioners decline training to improve management of medically unexplained symptoms? J Gen Intern Med 2007;22(5):565-571.

[129] Schweickhardt A, Larisch A, Fritzsche K. Differentiation of somatizing patients in primary care: why the effects of treatment are always moderate. The Journal of Nervous and Mental Disease 2005;193(12):813-819.

[130] Seivewright H, Green J, Salkovskis P, Barrett B, Nur U, Tyrer P. Cognitive–behavioural therapy for health anxiety in a genitourinary medicine clinic: randomised controlled trial. Br J Psychiatry 2008;193(4):332-337.

[131] Sharpe M, Peveler R, Mayou RA. The psychological treatment of patients with functional somatic symptoms: a practical guide. J Psychosom Res 1992(36):515-529.

[132] Shorter E, Abbey SE, Gillies LA, Singh M, Lipowski ZJ. Inpatient treatment of persistent somatization. Psychosomatics 1992;33(3):295-301.

[133] Slobbe LCJ, Smit JM, Groen J, Poos MJJC, Kommer GJ. Kosten van ziekten in Nederland 2007: trends in de Nederlandse zorguitgaven 1999-2010. Bilthoven: Rijksinstituut voor Volksgezondheid en Milieu (RIVM)/Centraal Bureau voor de Statistiek (CBS), 2011. RIVM-rapportnummer 270751023/2011.

[134] Smit F, Cuijpers P, Oostenbrink J, Batelaan N, De Graaf R, Beekman A. Costs of nine common mental disorders: implications for curative and preventive psychiatry. Journal of Mental Health Policy and Economics 2006;9(4):193-200.

[135] Smith GR, Monson RA, Ray DC. Patients with multiple unexplained symptoms: their characteristics, functional health, and health care utilization. Arch Intern Med 1986;146(1):69-72.

[136] Smith RC, Gardiner JC, Lyles JS, Sirbu C, Dwamena FC, Hodges A, Collins C, Lein C, Given CW, Given B, Goddeeris J. Exploration of DSM-IV criteria in primary care patients with medically unexplained symptoms. Psychosom Med 2005;67(1):123-129.

[137] Soeteman DI, Hakkaart-van Roijen L, Verheul R, Busschbach JJV. The economic burden of personality disorders in mental health care. J Clin Psychiatry 2008;69(2):259-265.

[138] Soeteman DI, Verheul R, Busschbach JJV. The burden of disease in personality disorders: diagnosis-specific quality of life. J Personal Disord 2008;22(3):259-268.

[139] Soper DS. A-priori sample size calculator for multiple regression: online software. http://www.danielsoper.com/statcalc3, 2011.

[140] Speckens AEM, Spinhoven P, Hawton KE, Bolk JH, Van Hemert AM. Cognitive behavioural therapy for medically unexplained physical symptoms: a pilot study. Behavioural and Cognitive Psychotherapy 1996;24(1):1-16.

[141] Speckens AEM, Spinhoven P, Van Rood YR. Protocollaire behandeling van patiënten met onverklaarde lichamelijke klachten: cognitieve gedragstherapie. In: GPJ Keijsers, A van Minnen, CAL Hoogduin, editors. Protocollaire behandelingen in de ambulante geestelijke gezondheidszorg 2. Houten/Diegem: Bohn Stafleu Van Loghum, 1999. pp. 199-236.

[142] Speckens AEM, Van Hemert AM, Bolk JH, Hawton KE, Rooijmans HGM. The acceptability of psychological treatment in patients with medically unexplained physical symptoms. J Psychosom Res 1995;39(7):855-863.

[143] Speckens AEM, Van Hemert AM, Bolk JH, Rooijmans HGM, Hengeveld MW. Unexplained physical symptoms: outcome, utilization of medical care and associated factors. Psychol Med 1996;26(4):745-752.

[144] Speckens AEM, Van Hemert AM, Spinhoven P, Hawton KE, Bolk JH, Rooijmans HGM. Cognitive behavioural therapy for medically unexplained physical symptoms: a randomised controlled trial. Br Med J 1995;311(7016):1328-1332.

[145] Sprangers MAG, De Regt EB, Andries F, Van Agt HME, Bijl RV, De Boer JB, Foets M, Hoeymans N, Jacobs AE, Kempen GIJM, Miedema HS, Tijhuis MAR, De Haes HCJM. Which chronic conditions are associated with better or poorer quality of life? J Clin Epidemiol 2000;53(9):895-907.

[146] Statistics Netherlands. Verschillen in cijfers over huisartscontacten tussen POLS-Gezondheid en de statistiek ‹Geregistreerde contacten met de huisarts›. Den Haag/Heerlen: Statistics Netherlands/Centraal Bureau voor de Statistiek, 2009.

[147] Statistics Netherlands. Sterfte; geslacht en leeftijd (op 31 december), per week. http://statline.cbs.nl/StatWeb/publication/default.aspx?DM=SLNL&PA=03759ned&D1=0-2&D2=129-132&D3=0-4&D4=%28l-1%29-l&VW=T, 2010.

[148] Statistics Netherlands. Bevolking; kerncijfers (2007). http://statline.cbs.nl/StatWeb/publication/?DM=SLNL&PA=37296ned&D1=0-51&D2=57&VW=T, 2012.

[149] Stolk EA, Pickee SJ, Ament AHJA, Busschbach JJV. Equity in health care prioritisation: an empirical inquiry into social value. Health Policy 2005;74():343-355.

[150] Stolk EA, Van Donselaar G, Brouwer WBF, Busschbach JJV. Reconciliation of economic concerns and health policy: illustration of an equity adjustment procedure using proportional shortfall. Pharmacoeconomics 2004;22(17):1097-1107.

[151] Stone J, Wojcik W, Durrance D, Carson A, Lewis S, MacKenzie L, Warlow CP, Sharpe M. What should we say to patients with symptoms unexplained by disease? The "number needed to offend". Br Med J 2002;325(7378):1449-1450.

[152] Sumathipala A. What is the evidence for the efficacy of treatments for somatoform disorders? A critical review of previous intervention studies. Psychosom Med 2007;69(9):889-900.

[153] Sumathipala A, Siribaddana S, Abeysingha MRN, De Silva P, Dewey M, Prince M, Mann AH. Cognitive behavioural therapy v. structured care for medically unexplained symptoms: randomised controlled trial. The British Journal of Psychiatry 2008;193(1):51-59.

[154] Sumathipala A, Siribaddana S, Hewege S, Sumathipala K, Prince M, Mann A. Understanding the explanatory model of the patient on their medically unexplained symptoms and its implication on treatment development research: a Sri Lanka Study. BMC Psychiatry 2008;8:54.

[155] Teckle P, Peacock S, McTaggart-Cowan H, Van der Hoek K, Chia S, Melosky B, Gelmon K. The ability of cancer-specific and generic preference-based instruments to discriminate across clinical and self-reported measures of cancer severities. Health and Quality of Life Outcomes 2011;9:106.

[156] Toft T, Rosendal M, Ørnbøl E, Olesen F, Frostholm L, Fink P. Training general practitioners in the treatment of functional somatic symptoms: effects on patient health in a cluster-randomised controlled trial (the Functional Illness in Primary Care Study). Psychother Psychosom 2010;79(4):227-237.

[157] Uguz F, Engin B, Yilmaz E. Axis I and Axis II diagnoses in patients with chronic idiopathic urticaria. J Psychosom Res 2008;64(2):225-229.

[158] Van den Hout AHC, Kole-Snijders AMJ. Cognitieve behandelingen. In: JWS Vlaeyen, PHTG Heuts, editors. Gedragsgeoriënteerde behandelingsstrategieën bij rugpijn. Houten/Diegem: Bohn Stafleu Van Loghum, 2000.

[159] Van der Feltz-Cornelis CM, Van Oppen P, Adèr HJ, Van Dyck R. Randomised controlled trial of a collaborative care model with psychiatric consultation for persistent medically unexplained symptoms in general practice. Psychother Psychosom 2006;75(5):282-289.

[160] Van der Mast RC. Onverklaarde lichamelijke klachten: een omvangrijk probleem, maar nog weinig zichtbaar in opleiding en richtlijnen. Ned Tijdschr Geneeskd 2006;150(12):686-692.

[161] Van Hemert AM, Hengeveld MW, Bolk JH, Rooijmans HGM, Vandenbroucke JP. Psychiatric disorders in relation to medical illness among patients of a general medical out-patient clinic. Psychol Med 1993;23(1):167-173.

[162] Van Rood Y, Visser S. Principes van cognitieve gedragstherapie in de GGZ. In: C Van der Feltz-Cornelis, H van der Horst, editors. Handboek somatisatie: lichamelijk onverklaarde klachten in de eerste en tweede lijn. Utrecht: De Tijdstroom, 2008. pp. 269-289.

[163] Van Rood YR, Ter Kuile MM, Speckens AEM. Ongedifferentieerde somatoforme stoornis. In: P Spinhoven, TK Bouman, CAL Hoogduin, editors. Behandelingsstrategieën bij somatoforme stoornissen. Houten/Diegem: Bohn Stafleu Van Loghum, 2001. pp. 17-40.

[164] Van Rood YR, Van Es SM. Ontspanningsoefeningen: een handleiding met speciale aandacht voor het gebruik van ontspanningsoefeningen bij lichamelijk klachten. Leiden: Leids Universitair Medisch Centrum, 2001.

[165] Verhaak PFM, Meijer SA, Visser AP, Wolters G. Persistent presentation of medically unexplained symptoms in general practice. Fam Pract 2006; 23(4):414-420.

[166] Walters SJ, Brazier JE. Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D. Qual Life Res 2005;14(6):1523-1532.

[167] Ware JE, Kosinski M, Keller SD. SF-36 physical and mental health summary scales: a user›s manual. Boston, MA: New England Medical Center, The Health Institute, 1994.

[168] Ware JE, Snow KK, Kosinski M, Gandek B. SF-36 health survey: manual and interpretation guide. Boston, MA: New England Medical Center, The Health Institute, 1993.

[169] Watson JC, Geller SM. The relation among the relationship conditions, working alliance, and outcome in both process-experiential and cognitive-behavioral psychotherapy. Psychotherapy Research 2005;15(1-2):25-33.

[170] Zonneveld LNL. Draaiboek (trainers) ‹Omgaan met de gevolgen van onverklaarde lichamelijke klachten›. Vlaardingen/Rotterdam: Riagg Rijnmond/Erasmus MC Afdeling Medische Psychologie en Psychotherapie, 2005.

[171] Zonneveld LNL. Group training for patients with unexplained physical symptoms. http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=1609: Nederlands Trial Register, 2009.

[172] Zonneveld LNL, Duivenvoorden HJ, Passchier J, Van 't Spijker A. Tailoring a cognitive behavioural model for unexplained physical symptoms to patient's perspective: a bottom-up approach. Clinical Psychology and Psychotherapy 2010;17(6):528-535.

[173] Zonneveld LNL, Van ‹t Spijker A, Passchier J, Van Busschbach JJ, Duivenvoorden HJ. The effectiveness of a training for patients with unexplained physical symptoms: protocol of a cognitive behavioral group training and randomized controlled trial. BMC Public Health 2009;9:251.

[174] Zonneveld LNL, Van 't Spijker A, Van Busschbach JJ. Bevorderen van gepaste zorg voor patiënten met onverklaarde lichamelijke klachten: een voorbeeld. GZ-psychologie 2012;4(2):10-15.

[175] Zonneveld LNL, Van Rood YR, Timman R, Kooiman CG, Van 't Spijker A, Busschbach JJV. Effective group training for patients with unexplained physical symptoms: a randomized controlled trial with a non-randomized one-year follow-up. PLoS ONE 2012;7(8):e42629.

Summary

Background

Unexplained Physical Symptoms (UPS) are physical symptoms that cannot be fully explained by a known medical condition. These symptoms can be classified as a DSM-IV somatoform disorder, if they are not intentionally produced or feigned, cause clinically significant distress or impairment in functioning, persist at least six months, and are not better accounted for by other DSM-IV classifications. The most common somatoform disorders are undifferentiated somatoform disorder with a prevalence of 13 percent and chronic pain disorder with a prevalence of 1.6 percent. In only 25 percent of the patients with a somatoform disorder, the symptoms recover or improve spontaneously.

Low quality of life and high societal costs often prevail with UPS. In medical subspecialty clinics or mental health centers, cognitive-behavioral therapy has been shown to improve quality of life and to decrease costs. However, this therapy is not easily accessible to patients, as the treatment capacity of specialized centers is limited and/or because patients refuse to be referred to mental health services. A possible reason for patients' rejection might be that such a referral suggests 'it is all in their mind', by which they feel offended. In their perspective, psychosocial problems such as a depression are the consequences and not the causes of their UPS.

The aims of the study on which this thesis is based were the following:

1 evaluating how quality of life of patients with UPS and societal costs associated with them relate to corresponding data in other patient groups (Chapter 2);
2 developing a group training for patients with UPS tailored to their perspective and conducted by secondary community mental health services reaching out into primary care (Chapters 3-5);
3 investigating its effectiveness and the preservation of this effect over a time period of one year (Chapter 6);
4 examining whether diagnostics and assessment for this training are useful (Chapter 7);
5 evaluating the cost-effectiveness of this training (Chapter 8).

Methods

In this study, 162 patients with UPS classified as an undifferentiated somatoform disorder or as a chronic pain disorder were randomized either to the group training or to a waiting list after they had completed the baseline measurement (T_0). The second measurement (T_1) was made directly after the training (13 weeks), or after the same period for those on the waiting list. After this second measurement, patients, who had been randomized to the waiting list and had waited, started the training. Patients, who attended the training

directly after randomization or after the waiting period, were followed-up three months after the training (T_2), and again one year after the training (T_3).

The group training is a cognitive-behavioral training called 'Coping with the consequences of unexplained physical symptoms'. This training comprises 13 weekly two-hour sessions, which are verbatim described in a manual. The sessions are tailored to patients' perspective on UPS and their treatment goals. To link to patients' perspective, biopsychosocial factors are consistently described as consequences and not as causes of UPS, which are by definition unknown. The existence and persistence of these consequences are justified because of their benign short-term effects on UPS, functioning or coping. However, in the long run, most consequences have negative effects. Therefore, changes in physiological, behavioral, emotional, cognitive and/or social reactions to UPS resulting in more benign long-term consequences are needed. These changes are stimulated by using firstly psycho-education in physical terms, subsequently behavioral techniques and lastly cognitive techniques in the training.

By defining the causes of UPS as unknown and by justifying its consequences, patients are released from being blamed (exonerated) for the development and maintenance of their UPS. The suggestion that 'it is all in the mind' is prevented. By linking to patients' perspective, the training matches patients' most important reason for seeking help, which is being supported by their healthcare provider. By optimizing the reactions to UPS, functioning and coping are improved, which are the other two most important reasons of patients for seeking help. In line with patients' reasons for seeking help, the aim of training is to improve health-related quality of life.

The effectiveness of the training was measured using self-report questionnaires on the quality of life (SF-36), on physical and psychological complaints (SCL-90-R), and on societal costs (TiC-P). The primary outcome for the effectiveness of training was the physical and the mental summary scales of the SF-36.

Psychiatric comorbidity was measured using a semi-structured interview on the major DSM-IV Axis I diagnoses (SCID-I/P), and a self-report questionnaire on personality-disorder characteristics (VKP).

Results

Patients with UPS reported poor quality of life in the physical and social domains, and relatively better quality of life in the mental domain. When summarizing the quality of life into a one single weighted score, the quality of life of patients with UPS appeared to be among the poorest compared with those of other patient groups. (Chapter 2)

Societal costs associated with UPS resulted from the use of healthcare services and productivity loss in labor and domestic tasks. These societal costs were higher than those of most other patient groups. (Chapter 2)

A cognitive-behavioral group training for patients with UPS aiming at improving quality of life of patients could be implemented in *medical* settings by a secondary community mental health service. For this implementation, the mental health service sought close collaboration with medical services. (Chapters 3-5)

The training improved patients' quality of life in the physical domain, which was the domain patients experienced as most burdensome at baseline. Also, after the training, patients randomized to the training reported a better physical, emotional, and social functioning, less pain and better functioning despite pain, more vitality, less physical symptoms and less sleep difficulties than patients randomized to the waiting list. During the follow-ups, there were no relapses. (Chapter 6)

Psychiatric comorbidity assessed at baseline did not consistently predict the outcome of the training over time. (Chapter 7)

The group training was cost-effective. The cost-effectiveness ratio dropped below €30,000 per QALY at 18 months. This means that, after 18 months, the net cost of the training was lower than the cost which society is willing to pay for an increased quality of life. (Chapter 8)

Conclusions

Patients with UPS are in great need of care in view of their poor quality of life, which justifies the allocation of sufficient resources for research and treatment. As they already have a high healthcare utilization resulting in high societal costs, the question raises whether resources should be redistributed to create more effective treatments and, preferably, cost-effective treatments. The cognitive-behavioral group training tailored to patients' perspective and called 'Coping with the consequences of unexplained physical symptoms' is effective and also cost-effective. Its effectiveness is achieved without elaborate diagnostics and assessment to allocate patients. This suggests that a redistribution of resources to implement this training on a large scale by mental healthcare providers will be in the interest of both patients and society.

Samenvatting

Achtergrond

Onverklaarde lichamelijke klachten zijn lichamelijke klachten die niet of niet voldoende verklaard kunnen worden door een bekende lichamelijke aandoening. Deze klachten kunnen geclassificeerd worden als een DSM-IV somatoforme stoornis, als ze niet met opzet veroorzaakt of voorgewend worden, in significante mate lijden of beperkingen in het functioneren veroorzaken, tenminste 6 maanden duren en niet toe te schrijven zijn aan een andere DSM-IV classificatie. De meest voorkomende somatoforme stoornissen zijn de ongedifferentieerde somatoforme stoornis met een prevalentie van 13% en de chronische pijnstoornis met een prevalentie van 1,6%. In slechts 25% van de patiënten met een somatoforme stoornis genezen of verminderen de lichamelijk klachten spontaan.

Een slechte kwaliteit van leven en hoge maatschappelijke kosten komen vaak voor bij onverklaarde lichamelijke klachten. In de specialistische medische centra en in de geestelijke gezondheidszorg blijkt cognitieve gedragstherapie de kwaliteit van leven te kunnen verbeteren en kosten te kunnen verminderen. Deze therapie is echter niet gemakkelijk toegankelijk voor patiënten, omdat de behandelcapaciteit van specialistische centra beperkt is en/of omdat patiënten een verwijzing naar de geestelijke gezondheidszorg afslaan. Een mogelijke reden om dit aanbod af te slaan zou kunnen zijn, dat een dergelijke verwijzing suggereert dat het 'tussen de oren zit', waardoor patiënten zich niet begrepen voelen. In hun perspectief zijn psychosociale problemen, zoals een depressie, de gevolgen en niet de oorzaken van hun lichamelijke klachten.

De doelen van het onderzoek, waarop dit proefschrift is gebaseerd, waren de volgende:

1 het evalueren van de kwaliteit van leven en de maatschappelijke kosten van patiënten met onverklaarde lichamelijke klachten door deze te vergelijken met andere patiëntengroepen (Hoofdstuk 2);
2 het ontwikkelen van een cursus voor patiënten met onverklaarde lichamelijke klachten, die aansluit bij het perspectief van deze patiëntengroep en die door een Riagg in een anderhalve lijnszorg uitgevoerd kan worden (Hoofdstukken 3-5);
3 het onderzoeken van de effectiviteit van deze cursus en het voortduren van dit effect gedurende een jaar (Hoofdstuk 6);
4 het onderzoeken of indicatiestelling voor deze cursus zinvol is (Hoofdstuk 7);
5 het evalueren van de kosten-effectiviteit van deze cursus (Hoofdstuk 8).

Methoden

In dit onderzoek zijn 162 patiënten met onverklaarde lichamelijke klachten, die geclassificeerd waren als een ongedifferentieerde somatoforme stoornis of als een chronische pijnstoornis, gerandomiseerd naar de cursus of de wachtlijst, nadat ze de voormeting (T_0) hadden afgerond. Direct na het volgen van de cursus (13 weken) of na

het wachten op de wachtlijst vond de nameting (T_1) plaats. Na deze nameting mochten de patiënten, die op de wachtlijst stonden en gewacht hadden, met de cursus beginnen. Bij alle cursisten werd er een vervolgmeting gedaan op drie maanden na de cursus (T_2) en vervolgens op een jaar na de cursus (T_3).

De cursus is een cognitief-gedragsmatige groepscursus genaamd 'Omgaan met de gevolgen van onverklaarde lichamelijke klachten'. Deze cursus omvat 13 wekelijkse bijeenkomsten van twee uur, die verbatim beschreven staan in een draaiboek. De bijeenkomsten zijn toegesneden naar het perspectief van patiënten op hun klachten en hun behandeldoelen. Voor de aansluiting bij het patiëntenperspectief worden biopsychosociale factoren consistent beschreven als de gevolgen en niet als de oorzaken van onverklaarde lichamelijke klachten, die immers per definitie onbekend zijn. Het ontstaan en het voortduren van deze gevolgen worden gerechtvaardigd door hun gunstige korte termijn effect op de klachten, het functioneren en de coping. Op de lange termijn worden de meeste gevolgen echter ongunstig. Om ook op de lange termijn meer gunstige gevolgen te hebben kan een verandering in de lichamelijke, gedragsmatige, emotionele, cognitieve en/of sociale reacties op de lichamelijke klachten noodzakelijk zijn. Om deze verandering te stimuleren wordt in de cursus eerst psycho-educatie in fysieke termen, vervolgens gedragsmatige technieken en tenslotte cognitieve technieken aangeboden.

Door de oorzaak van de lichamelijke klachten onbekend te stellen en de gevolgen ervan te rechtvaardigen worden patiënten niet verantwoordelijk gemaakt (ontschuldigd) voor het ontstaan en voortduren van hun onverklaarde lichamelijke klachten. Dit voorkomt de suggestie, dat 'het tussen de oren zit'. Door op deze manier aan te sluiten bij het perspectief van patiënten voorziet de cursus in het belangrijkste behandeldoel voor patiënten, namelijk steun van een hulpverlener. Door het optimaliseren van de reacties op de onverklaarde lichamelijke klachten worden het functioneren en de coping van patiënten verbeterd, wat twee andere belangrijke redenen van patiënten zijn om hulp te zoeken. Overeenkomstig met deze redenen om hulp te zoeken is het doel van de cursus dan ook het verbeteren van de kwaliteit van leven.

De effectiviteit van de cursus werd gemeten door zelf-rapportage vragenlijsten naar kwaliteit van leven (SF-36), naar lichamelijke en psychische klachten (SCL-90-R) en naar maatschappelijke kosten (TiC-P). De primaire uitkomstmaten voor de effectiviteit van de cursus waren de twee totaalscores voor kwaliteit van leven gemeten met de SF-36.

Psychische comorbiditeit werd gemeten door een semi-gestructureerd interview naar de voornaamste DSM-IV As I classificaties (SCID-I/P) en een zelf-rapportage vragenlijst naar kenmerken van de persoonlijkheid (VKP).

Resultaten

Patiënten met onverklaarde lichamelijke klachten rapporteerden een slechte kwaliteit van leven in het fysieke en sociale domein en een relatief betere kwaliteit van leven in het mentale domein. Als hun kwaliteit van leven werd samengevat in een gewogen score, dan bleek deze één van de slechtste te zijn in vergelijking met die van andere patiëntengroepen. (Hoofdstuk 2)

De maatschappelijke kosten gerelateerd aan onverklaarde lichamelijke klachten zijn het gevolg van het zorggebruik en van productieverliezen in werk en huishoudelijke taken. Deze maatschappelijke kosten waren in vergelijking met die van andere patiëntengroepen één van de hoogste. (Hoofdstuk 2)

Een cognitief-gedragsmatige cursus voor patiënten met onverklaarde lichamelijke klachten met als doel het verbeteren van kwaliteit van leven kon in *medische* settings geïmplementeerd worden door een Riagg. Voor deze implementatie zocht de Riagg een nauwe samenwerking met instellingen in de medische gezondheidszorg. (Hoofdstukken 3-5)

De cursus verbeterde de kwaliteit van leven van patiënten in het fysieke domein, wat het domein is waarin patiënten de meeste lijdensdruk ervoeren bij de voormeting. Patiënten, die de cursus gevolgd hadden, rapporteerden na de cursus ook een beter fysiek, emotioneel, en sociaal functioneren, minder pijn en beter functioneren ondanks de pijn, meer vitaliteit, minder lichamelijke symptomen en minder slaapproblemen dan de wachtlijstgroep na de wachtperiode. De vervolgmetingen gaven geen terugval weer. (Hoofdstuk 6)

Psychische comorbiditeit gemeten tijdens de voormeting voorspelde niet op consistente wijze de uitkomsten van de cursus over de tijd. (Hoofdstuk 7)

De cursus was kosten-effectief. Na 18 maanden was de kosten-effectiviteit ratio lager dan €30.000 per QALY. Dit betekent dat de netto kosten voor de cursus na 18 maanden lager waren dan de kosten die de maatschappij bereid is te betalen voor een verbetering in kwaliteit van leven. (Hoofdstuk 8)

Conclusies

Patiënten met onverklaarde lichamelijke klachten hebben een grote hulpbehoefte gezien hun slechte kwaliteit van leven. Dit rechtvaardigt de toewijzing van voldoende middelen voor onderzoek en behandeling. Aangezien het zorggebruik van patiënten met onverklaarde klachten al groot is, wat resulteert in grote maatschappelijke kosten, rijst echter de vraag of de middelen niet herverdeeld zouden moeten worden om effectievere en, bij voorkeur, kosten-effectieve behandelingen te creëren. De cognitief-gedragsmatige cursus 'Omgaan met de gevolgen van onverklaarde lichamelijke klachten', die aansluit

bij het patiëntenperspectief, is effectief en ook kosten-effectief. Deze effectiviteit wordt bereikt zonder uitgebreide indicatiestelling. Dit wijst erop, dat een herverdeling van middelen ten gunste van de cursus zowel in het belang is voor patiënten als voor de maatschappij.

Dankwoord

Dankwoord

Op deze plaats wil ik een ieder bedanken die op directe of indirecte wijze een bijdrage heeft geleverd aan dit proefschrift.

Weledelgeleerde heer Methorst, beste Hans. Jij was en bent nog steeds voor mij als voormalig werkbegeleider van de Postdoctorale Opleiding tot Klinisch Psycholoog en voormalig afdelingshoofd van de afdeling Psychotherapie van Riagg Rijnmond een heel belangrijk rolmodel. Ik denk nog steeds regelmatig hoe zou Hans dit aangepakt hebben. Jouw betrouwbaarheid, integriteit en wijsheid maakten jou tot een bijzonder persoon, bij wie ik mezelf kon zijn en met al mijn vragen terecht kon. Je was iemand die zich aan zijn woord hield, niet voor eigen belang ging en oog had voor het perspectief van de ander. Je hebt me laten geloven in mezelf door het grote vertrouwen, dat je me onvoorwaardelijk gaf op alle aspecten van ons vak. Jouw woorden "Moet je doen!" en "Verstandig!", waarin je dit onvoorwaardelijk vertrouwen verwoordde, liggen nog steeds vers in mijn geheugen. Ik hoop dat ik met het afronden van mijn proefschrift je vertrouwen waar heb kunnen maken. Ik ben er trots op, dat ik één van je vele opleidelingen en een teamlid van jouw afdeling heb mogen zijn. Wat zou het mooi zijn geweest, als ik dit persoonlijk aan jou gezegd zou kunnen hebben en we samen zouden hebben kunnen terugkijken op het opleidings- en promotietraject. Helaas stond Petrus eerder voor de deur.

Hooggeleerde heer Trijsburg, beste Wim. Je was mijn praktijkopleider vanuit Medische Psychologie & Psychotherapie, Erasmus MC en supervisor van het wetenschappelijk onderzoek binnen het kader van de Postdoctorale Opleiding tot Klinisch Psycholoog. Tijdens deze opleiding gaf je al de mogelijkheid van promoveren aan en na mijn opleiding zag je kansen om dit traject spoedig in te zetten. De inkt van mijn diploma was dan ook nog niet droog of we zaten samen met Jos Lamé als Raad van Bestuur van Riagg Rijnmond om de tafel om zijn akkoord voor een promotietraject te vragen. In geanimeerd gesprek introduceerde je me als science practitioner en koploper voor de academisering van Riagg Rijnmond in samenwerking met afdeling Medische Psychologie & Psychotherapie van Erasmus MC. Ik had ook graag met jou willen terugkijken en je voor deze introductie die tot dit proefschrift heeft kunnen leiden willen bedanken. Helaas was Petrus me alweer voor.

Hooggeleerde heer Passchier, beste Jan. Na het overlijden van Wim nam jij het promotorschap over. Door het overlijden van Wim en ook dat van Hans waren de dragers van het wetenschappelijk onderzoek bij patiënten met onverklaarde lichamelijke klachten weggevallen. Over de verdeling van financiële middelen werd hierdoor opnieuw en helaas anders beslist, waardoor het afronden van dit onderzoek in gevaar kwam.

Het lukte je om het belang en kracht van dit onderzoek zodanig over het voetlicht te brengen, dat ik mijn dataverzameling kon afronden. Amsterdam lonkte echter naar je en je werd decaan bij de Faculteit der Psychologie en Pedagogiek van de Vrije Universiteit Amsterdam, waardoor je helaas mijn promotor niet meer kon zijn.

Hooggeleerde heer Van Busschbach, beste Jan. Jij nam als promotor het promotieonderzoek over op het moment, dat er geen financiën voor het onderzoek waren. Als professor met kosteneffectiviteit hoog in het vaandel zou dit financiële plaatje je hebben kunnen afschrikken, maar het tegenovergestelde was waar. Je vond het wel een uitdaging. En je had het lef en de vooruitziende blik van een beurshandelaar van deze tijd om in dit onderzoek te investeren. Je bent een kei in onderhandelen, partijen om en alle belangen op tafel te krijgen en je bent toeschietelijk om tot een overeenkomst te komen. Door dit lef, het vertrouwen in het onderzoek en in mij als uitvoerder ervan, je steunende coaching en je investeringen, waaronder een deeltijdaanstelling bij de afdeling Medische Psychologie en Psychotherapie, heb ik het promotietraject kunnen afronden en op een steeds hoger plan kunnen brengen. Dit proefschrift had zonder de -door jou- geboden kansen niet tot stand kunnen komen. Mijn dank hiervoor is groot.

Weledelzeergeleerde heer Van 't Spijker, beste Adriaan. Je bent als copromotor aan het lange afstandpad toegevoegd. Je hield van grote stappen. Je had het vertrouwen, dat ik de tussenliggende stappen zelf kon invullen. Toen het einde van het lange afstandpad in het zicht kwam en ik het in een sprintje wilde finishen, baande je het pad hiervoor uit en kon ik sprinten. Van jouw manier van loslaten en alleen interveniëren waar nodig kan ik nog veel leren.

Weledelzeergeleerde heer Duivenvoorden, beste Hugo. Je hebt vaak aan het rad gedraaid om patiënten te randomiseren. Ook bij het zoeken van statistische analyses hield je het rad draaiend. Het was aan mij om het rad stil te zetten bij die statistische analyse, die zo simpel als mogelijk, zo complex als nodig was en beargumenteerbaar en uitvoerbaar voor mij was. Je hebt me hiermee de mogelijkheden gegeven om mijn kennis van de statistische analyses te vergroten en me hiermee meer vertrouwd te maken.

Weledelzeergeleerde heer Timman, beste Reinier. In korte tijd had je de data van dit onderzoek in je vingers en liet je SPSS regressiemodellen voor de effectiviteit maken. In heldere en bondige bewoordingen kon je me duidelijk maken hoe mooi deze modellen voor het wetenschappelijk onderzoek waren. De resultaten uit de eerdere analyses werden hiermee bevestigd en nog steviger neergezet.

Weledelgeleerde heer Visser, beste Martijn. Kosteneffectiviteit wordt door behandelaars vaak synoniem gezien aan het verminderen van de kwaliteit van patiëntenzorg ten gunste van het prijskaartje. Je hebt me kunnen boeien voor deze materie, zodat ik nu weet dat dit vooroordeel onjuist is.

Weledelzeergeleerde vrouwe Van Rood, beste Yanda. Je hebt het gevolgenmodel in Nederland groot gemaakt en de kwaliteit van patiëntenzorg hiermee een grote dienst bewezen. Tot mijn blijdschap heb je mijn initiatief om de reikwijdte ervan te vergroten ondersteund. De gesprekken over de zin en de onzin om hiervoor het gevolgenmodel te modificeren waren inspirerend en hebben tot een betere theorievorming erover geleid. Ik hoop dat onze voettocht een vervolg heeft, zodat we deze patiëntengroep nog beter op de kaart kunnen zetten.

Weledelzeergeleerde heer Kooiman, beste Kees. Je voegde je bij onze voettocht als nieuw afdelingshoofd van de afdeling Psychotherapie van Riagg Rijnmond, toen het gehele pad al was uitgepaald en een groot gedeelte van het traject was afgelegd. Je vragen hierover hebben tot een betere verwoording van de gemaakte keuzes geleid. Ik waardeer het ten zeerste, dat we het pad samen hebben kunnen uitlopen.

Hooggeleerde vrouwe Sprangers, beste Mirjam. Jouw scherpzinnigheid en mooi taalgebruik maken een manuscript in korte tijd to-the-point en transparant. Ik hoop dat er nog vele manuscripten met jou mogen volgen.

Weledelgeleerde vrouwen Van der Hoeven-Seubring, Coolen, Den Dekker-Mast, Buijks, De Niet, Blok, Boden-van den Brand, beste Aike, Carola, Jeanette, Hanneke, Judith, Janine en Ingrid. Jullie hebben op de meest onmogelijke momenten en wisselende locaties gestructureerde interviews afgenomen. Of de patiënten nu al dan niet kwamen opdagen, jullie waren er. Aan jullie was de moeilijke taak om daarna te besluiten om patiënten te includeren of te excluderen. Dit is een lastige taak, waarin jullie ruimhartig de cursus aan patiënten hebben aangeboden.

Weledelgeleerde vrouwen Lievaart, Van Jaarsveld en Kraut, beste Caroline, Astrid en Lieke. Bepakt en bezakt met laptop, beamer, flappen, CD's, draai- en werkboeken gingen jullie op pad naar de medische settings om de cursus aan patiënten te geven. Bedankt dat jullie dit avontuur aandurfden en jullie boeiende ervaringen met me wilden delen.

Mijnheer Van Pelt, beste BJ. Je hebt de data van de TiC-P ingevoerd, waardoor ik mij kon richten op het analyseren van de rest van data. Hiermee heb je mijn rugzak lichter gemaakt.

Mevrouw Beukers, beste Puck. Met jouw charmes wist je het prijskaartje te achterhalen, dat aan de cursus hing.

Weledelgeleerde heer Butterhoff, beste Jordi. Als hoofd van de poliklinische apotheek van het Academisch Medisch Centrum heb je meegedacht over de talrijke medicamenten, die door mijn onderzoeksgroep gebruikt werden. Je hebt me inzicht gegeven in een klein gedeelte van het omvangrijke specialisme, dat de farmacie omvat. Hierdoor heb ik de medicamenten, die gebruikt werden door mijn onderzoeksgroep, beter op waarde kunnen schatten.

Weledelgeleerde heer Alexander, dear David. Your dedication to make English as readable and as sound as possible, and your patience to come to this end have been very educational and inspiring.

Hooggeleerde heer Spinhoven, beste Philip. Je hebt de start van het voorliggende wetenschappelijk onderzoek in het kader van mijn Postdoctorale Opleiding tot Klinisch Psycholoog al met mooie woorden beoordeeld. Tot mijn groot genoegen wilde je ook plaatsnemen in de Kleine Commissie, zodat ik je ook kon laten zien wat het eindproduct geworden is. Opnieuw mocht dit wetenschappelijk onderzoek je goedkeuring ontvangen. Dank voor de steun, die je me op verschillende momenten tijdens het onderzoekstraject hebt gegeven. Ik ben nieuwsgierig naar jouw vragen als deskundige op het gebied van somatoforme stoornissen, die tot verdere en boeiende verdieping in dit onderwerp kunnen leiden.

Hooggeleerde heren Hoogendijk en Stam. Ik wil jullie bedanken voor het plaatsnemen in de Kleine Commissie en ben jullie erkentelijk voor het goedkeuren van dit proefschrift.

Hooggeleerde vrouwe De Haes, beste Hanneke. In de laatste fase van mijn promotie kwam de vacature voor de functie van Klinisch Psycholoog bij jouw afdeling Medische Psychologie voorbij. In 1999 had ik al met veel plezier als postdoctorale stagiaire op jouw afdeling gewerkt. Ik had je afdeling leren kennen als een gedegen afdeling, die patiëntenzorg, wetenschappelijk onderzoek en onderwijs op hoog niveau verzorgde. Ik ben trots, dat je opnieuw hebt gekozen om mij deel te laten maken van je veelzijdige afdeling en dat ik een beroep mag doen op je heldere kijk op zaken. Tot mijn blijdschap wilde je in de Grote Commissie plaatsnemen. Ik ben benieuwd wat jouw kijk op mijn proefschrift voor vragen oplevert.

Hooggeleerde heer Van Son, beste Maarten. Mijn eerste voetstappen als psycholoog in wording heb ik op de Universiteit Utrecht gezet. Door mijn voorkeur voor patiëntenzorg

en wetenschappelijk onderzoek in de Klinische psychologie en Gezondheidspsychologie kwam ik op jouw vakgroep terecht. Ik heb je leren kennen als een betrokken en integere man met een groot analyserend vermogen en kennis, van wie ik zowel in mijn doctorale- als postdoctorale opleidingen heb mogen leren. Ik ben vereerd, dat je wilde plaatsnemen in de Grote Commissie en kijk er naar uit om opnieuw door jou tot denken en een inspirerende dialoog te worden aangezet.

Hooggeleerde vrouwe Hunink. Ik wil u bedanken voor het plaatsnemen in de Grote Commissie.

Weledelgeleerde heer Lamé, beste Jos. Jij hebt mij als Raad van Bestuur van Riagg Rijnmond veel mogelijkheden gegeven om dit wetenschappelijk onderzoek te starten. Zonder deze steun en jouw enthousiasme voor nieuwe uitdagingen zou dit onderzoek niet zo uitgebreid van start hebben kunnen gaan. Een voorbeeld van jouw enthousiasme is jouw actie om het AD op mij af te sturen om ons nieuw Riagg initiatief voor patiënten met onverklaarde lichamelijke klachten 2 pagina's breed met foto in de regio te lanceren met een rood gloeiende telefoon, dito oren en een groot aantal patiënten voor de cursus als gevolg. Nog voor de voltooiing van de dataverzameling kon het promotietraject niet meer financieel ondersteund worden, maar jouw enthousiasme had me genoeg aangestoken om dit alsnog tot een goed einde te brengen.

Collega's van Riagg Rijnmond, beste allemaal. Jullie hebben alles van het begin op de voet gevolgd. In het bijzonder het secretariaat van afdeling Aanmelding en Consult heeft het startschot van dichtbij meegemaakt. Zij hebben vele aanmeldingen soms op bijzondere wijze aangenomen en vele gestructureerde interviews ingepland. Na dit startschot hebben we als Riagg over de verschillende afdelingen heen vele paden met elkaar belopen. Bij elke mijlsteen hebben we koffie met iets lekkers met elkaar gedronken. We hebben ook bakkies troost met elkaar gedeeld bij het overlijden van Nellie en Hans. Op mijn pad kwam een uitdagende werkplek bij het Academisch Medisch Centrum in Amsterdam langs, waardoor onze paden meer van elkaar afbogen. Jullie drukten me op het hart om jullie bij het afronden van dit lange afstandspad uit te nodigen om samen op de eindbestemming aan te komen. Jullie zitten in mijn hart, dus hoe zou ik deze eindbestemming zonder jullie kunnen bereiken?

Secretariaat van de afdeling Medische Psychologie en Psychotherapie van Erasmus MC. Regelmatig hebben jullie gepuzzeld om gaatjes in alle agenda's te vinden voor het overleg over de stukken van dit proefschrift. Miranda Spek deed deze puzzel vooral in de agenda van professor Van Busschbach, terwijl Margreet Langendoen dit heeft gedaan voor de agenda's van professoren Passchier en Trijsburg. Ingrid Immink heeft de lastige taak

gehad om het overlijden van professor Trijsburg aan me te vertellen. Jullie zorgvuldigheid en betrokkenheid hierin heb ik zeer gewaardeerd.

Collega's van de afdeling Medische Psychologie en Psychotherapie van Erasmus MC. De gastvrijheidverklaring onder professor Passchier bleek gastvrijheid in de breedste zin van het woord te zijn. Ik mocht te gast zijn op jullie feesten en partijen, waar jullie me gastvrij ontvingen. Als vanzelfsprekend betrokken jullie me in jullie gesprek, activiteiten en humor, waardoor de stap naar deeltijd collega onder professor Van Busschbach vertrouwd voelde.

Weledelgeleerde vrouwe Calff, beste Mart. Als groentje heb je me in 1999 aangenomen op een postdoctorale stageplek voor de patiëntenzorg in het Academisch Medisch Centrum. Het is heel uniek om meer dan 12 jaar later weer terug te komen op dezelfde werkplek. Zonder problemen konden we onze gesprekken weer oppakken, alsof 1999 gisteren was. Ik vond dit een hele bijzondere ervaring.

Collega's van de afdeling Medische Psychologie van het Academisch Medisch Centrum. Het is leuk om te merken, hoe onze brede interesse in patiëntenzorg, wetenschappelijk onderzoek en communicatie overeenkomen. Jullie interesse en het delen van ervaringen en dilemma's zijn een steun voor me.

Collega's van de polikliniek Pijngeneeskunde, het Pijncentrum en de afdeling Anesthesiologie van het Academisch Medisch Centrum. De polikliniek Pijngeneeskunde is een klein team, ingebed in de grote innovatieve afdeling Anesthesiologie. Door jullie gedrevenheid, korte lijnen, gelijkwaardigheid en samenwerking bereiken jullie een hoge kwaliteit zowel in patiëntenzorg als in wetenschappelijk onderzoek. Binnen korte tijd voelde ik me bij jullie thuis en ook de cursus voor patiënten met onverklaarde lichamelijke klachten vond snel bij jullie onderdak. Bedankt voor jullie steun, vertrouwen en de vele mogelijkheden die jullie me geven.

Verwijzers van het wetenschappelijk onderzoek. Jullie verwijzingen en inzet hebben dit wetenschappelijk onderzoek mogelijk gemaakt.

Deelnemende patiënten aan het wetenschappelijk onderzoek. Hartelijk dank voor jullie vertrouwen, enthousiasme in de cursus en trouw om telkens de lange reeks met vragen te beantwoorden. Zonder deze antwoorden had ik dit proefschrift niet kunnen schrijven.

De velen die mijn lichamelijke conditie tot hun doel maakten door mij modern te laten dansen in het Waddinxveense of door mij een choreo te laten doen op een spinningfiets,

op een rowapparaat, op zumba muziek, op Milon apparaten, met gewichten, met een bal en elastieken, of languit op een mat in het Goudse of door mij op een zacht matrasje te laten liggen in het Zoeterwoudse. Ik wil jullie bedanken voor de inspirerende en uiteenlopende manieren, die jullie me geboden hebben om mijn activiteiten af te wisselen, om uit te rennen en vervolgens uit te puffen.

Allen, die mij op het juiste moment een bemoedigend of lief gebaar en/of een motiverend of steunend woord aan mij gaven, maar ook diegene die een totaal ander onderwerp dan het proefschrift aansneden. Jullie hielpen me herinneren, dat er meer is dan werk alleen.

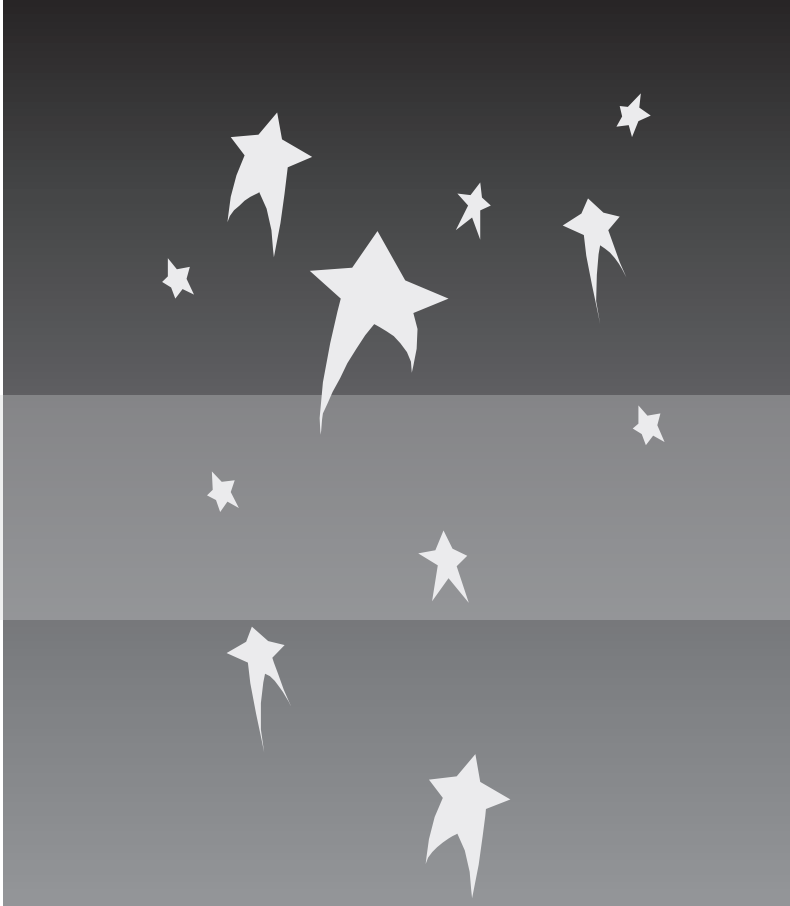
Mijnheer Zonneveld, lieve Leo, pap. Studeren was in het gezin, waar jij bent opgegroeid niet echt vanzelfsprekend. Je hebt hard geknokt, avondstudies gevolgd en je in het veld geprofileerd om op jonge leeftijd Handels- en later Wetenschapsattaché bij de Britse Ambassade te worden. Hoe anders was het bij ons thuis. Zowel Colinda, mijn zus, als ik hebben studeren als vanzelfsprekend mogen ervaren en hebben dit beiden lang na de reguliere trajecten voortgezet. In het promotietraject heb je mijn studie van heel dichtbij meegemaakt door mijn manuscripten op het Engels te controleren vanwege je uitstekende beheersing van de Engelse taal en je jarenlange coördinerend werk met Britse en Nederlandse academici vanuit de Britse Ambassade. Je ideaal was om uiteindelijk zelf te promoveren. Wat mij betreft, heb je dit door je grote betrokkenheid bij dit onderzoek verwezenlijkt.

Mevrouw Zonneveld-de Jong, lieve Coby, mam en mevrouw Zonneveld, lieve Colinda, zus. Jullie zagen al vroeg talenten in me. Colinda, jij zei tot ontsteltenis van pap en mam tegen de hoofdleraar van de basisschool, dat hij het niet in zijn hoofd moest halen om mij een MAVO-advies te geven en ik kwam in een HAVO-VWO brugklas terecht. Mam, jij kwam in de brugklas tot de ontdekking dat ik veel te veel televisie kon kijken, waardoor de brugklas met het VWO vervolgd werd. Jullie vroege ontdekkingen en stimulans hebben rechtstreeks tot een universitaire studie Psychologie geleid. Na deze studie had ik van jullie waarschijnlijk mogen stoppen en de nieuwe keuken, die al jaren op de planning staat, mogen aanschaffen. Hiermee zouden onze familiediners vaker dan op feestdagen kunnen plaatsvinden en zelfs deze diners schoten de laatste tijd erbij in. Hopelijk komt nu met de afronding van mijn proefschrift een nieuwe keuken snel in het zicht en kunnen de kookkunsten en daarmee het gezellig tafelen ook op postdoc niveau worden voortgezet.

Weledelzeergeleerde heer Hakkennes, lieve Edwin, echtgenoot, vriend en maatje. Behalve mijn veter-, tafel- en typediploma heb ik alle examens gedaan, toen ik jou al kende. Vanaf het begin heb je bij examens een steunende rol gehad. Ik herinner me dat ik op een VWO-examen verscheen en ik mijn boterhammen vergeten had, zonder enige

aarzeling haalde je een bruine boterham met kaas uit je lunchbox. Deze boterham gaf je aan mij, ofschoon ik toen niet meer was dan een klasgenoot. Bij een Psychologie-examen heb je een reuze kokosmakroon laten maken en talloze briefjes met lieve bemoedigingen onder mijn snelbinder van mijn fiets achtergelaten. Om deel te kunnen nemen aan de selectie van de GZ-opleiding kreeg ik een grote bos rode rozen met envelop. Tijdens de KP-opleiding was je aanwezig bij mijn presentatie van mijn wetenschappelijk onderzoek en ter afsluiting van de KP-opleiding kreeg ik een humoristische cartoon, waarop ik op de fiets zit met een boek in mijn hand. Ook tijdens het promoveren was je mijn steunpilaar. Je hebt als enige het draaiboek en het werkboek van de cursus 'Omgaan met de gevolgen van onverklaarde lichamelijke klachten' van voor naar achteren en terug gelezen om de leesbaarheid te controleren. Je brandde talloze ontspannings-CD's voor patiënten in de late uurtjes. Dit maakt dat je als dr.ir. in de elektrotechniek, ook een halve of misschien wel een hele psycholoog bent geworden. Naast de steun die je me geeft en het vertrouwen dat je in mij hebt, kunnen we samen door vele inspannende doch ontspannende wandel- en fietstochten ons hoofd weer leegmaken. De lange tocht van promoveren was niet mogelijk geweest zonder jouw steun, flexibiliteit en geloof in mijn werk en mij als persoon.

Curriculum Vitae



Curriculum Vitae

Lyonne Noël Lucia Zonneveld was born on the 11th of December 1971 in Reeuwijk, the Netherlands. She followed elementary school at 'De Rank' in Reeuwijk. From 1984 to 1990, she attended grammar school at the 'Christelijk Lyceum' in Gouda.

From 1990 to 1996, she studied Health Psychology at the University Utrecht in the Netherlands. During her study, she completed two Master's theses: a) Peri- and neonatal effects on behavioral problems in premature born children on the age of 9 and 10 years old, and b) Accuracy of children's pain memories. In order to complete the second Master's thesis, she joined the research group of Professor P.J. McGrath in the Pediatric Pain Lab of the 'Izaak Walton Killam Hospital for Children' and part of the Dalhousie University, in Halifax, Nova Scotia, Canada. This Master's thesis resulted in her first manuscript entitled 'Accuracy of children's pain memories', which was published in the journal *Pain*, July 1997. Before and after working in Canada, she did two internships involving adult patients: a) a clinical internship in assessment at the Department of Medical Psychology of the general hospital 'TerGooiziekenhuizen' (formerly known as 'Gooi-Noord') in Blaricum, and b) a clinical internship in treatment at the sanatorium, 'Prins Hendriksoord' in Laren. During her Masters, she worked as a teaching assistant in communication skills education for medical students in their third and fourth curriculum year at the Department of General Practice of University Utrecht.

After her graduation as a psychologist in 1996, she started as a volunteer at the phone-in counseling service for children in the greater Rotterdam area 'Kindertelefoon Rotterdam'. At the same time, she became a social worker at the crisis clinic for homeless people 'De Binnenvest' in Leiden. In 2000, she was selected to follow the Post-master Education towards Healthcare Psychologist at the 'PDO-GGZ Leiden/Rotterdam'. As part of this education, she did a clinical internship at a multidisciplinary centre for inpatient and outpatient treatment for those suffering from severe psychiatric problems 'MFC Zevenkamp' and at a clinic for acute psychiatry 'Intensieve Zorg'. Both clinics belong to the 'Parnassia Bavo Groep' (formerly known as 'Bavo RNO Groep') in Rotterdam.

After her graduation as a healthcare psychologist in 2002, she worked as a healthcare psychologist at the Departments of Consultation and Psychotherapy of the secondary community mental health service 'Riagg Rijnmond' in Vlaardingen/Rotterdam. In 2003, she was admitted to the Post-master Education towards Clinical Psychologist at the 'PDO-GGZ Leiden/Rotterdam'. Within the scope of this education, the foundation of the study on patients with unexplained physical symptoms described in this thesis was laid.

After her graduation as a clinical psychologist in 2007, she continued to work at 'Riagg Rijnmond' and she began her PhD study described in this thesis on a part-time basis at the Department of Medical Psychology and Psychotherapy of the Erasmus Medical Center / Erasmus University in Rotterdam. In the meantime, she finished her

education as a cognitive-behavioral therapist and became a registered therapist at the Dutch Association of Behavioral therapy and Cognitive therapy (VGCt).

Presently, she is working as a clinical psychologist, psychotherapist, and cognitive-behavioral therapist with patients suffering from pain at the Departments of Medical Psychology and Anesthesiology of the Academic Medical Center (AMC) / University of Amsterdam (UvA).

PhD Portfolio

PhD Portfolio

Name PhD student: Lyonne N.L. Zonneveld
Erasmus MC Department: Medical Psychology and Psychotherapy
Research School: Nihes
PhD period (including Post-master Education towards Clinical Psychologist): 2003-2012
Promotor: prof.dr. J.J. van Busschbach
Supervisor: dr. A. van 't Spijker

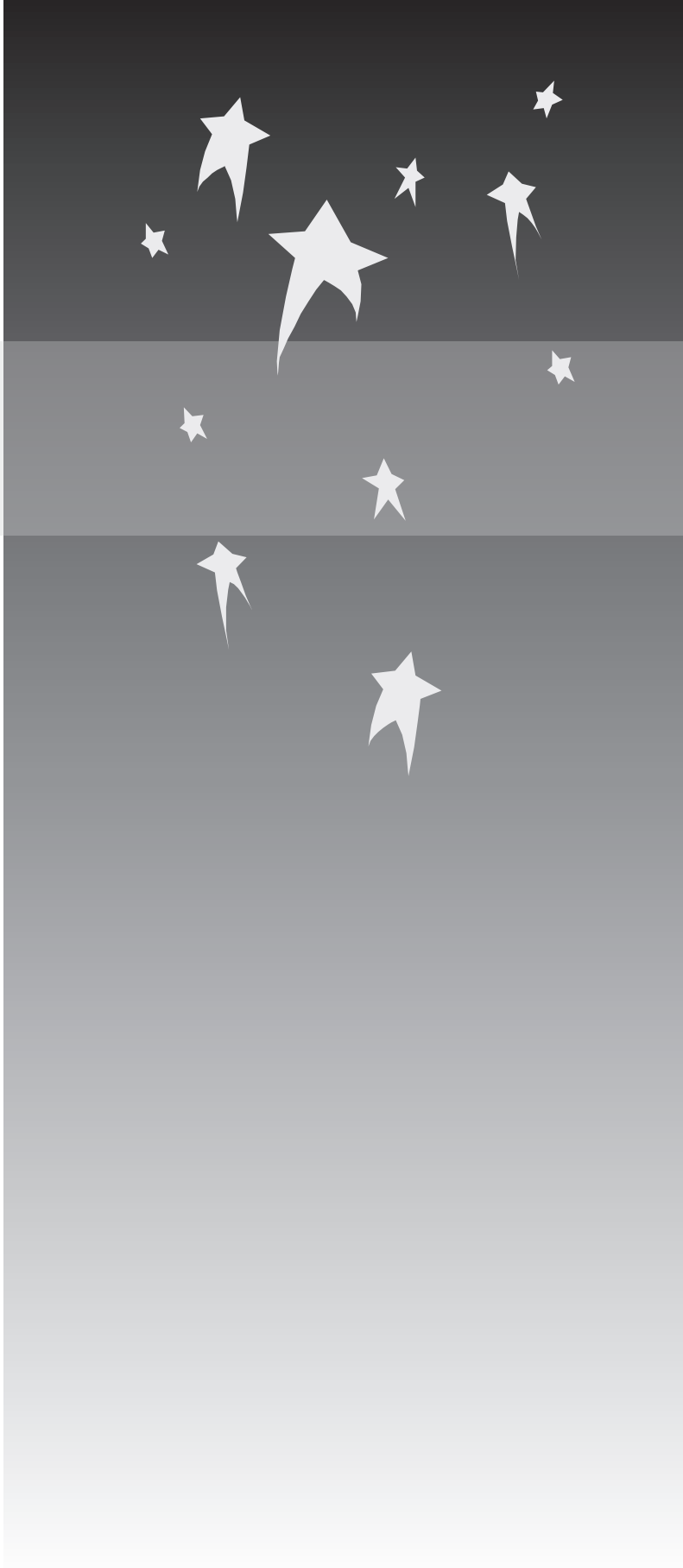
1. PhD training	Year	Contact hours (ECTS)
1.1 General academic skills		
Ethics and jurisdiction, PDO-GGZ Leiden/Rotterdam, the Netherlands.	2003-2006	30 (1.1)
Management and policy, PDO-GGZ Leiden/Rotterdam, the Netherlands.	2003-2006	30 (1.1)
Educational counseling and supervising, PDO-GGZ Leiden/Rotterdam, the Netherlands.	2003-2006	15 (0.5)
Professional identity of the clinical psychologist, PDO-GGZ Leiden/Rotterdam, the Netherlands.	2003-2006	15 (0.5)
English Biomedical Writing and Communication, Erasmus MC, Rotterdam, the Netherlands.	2010	37.5 (1.3)
1.2 Research skills		
Scientific training and innovation, PDO-GGZ Leiden/Rotterdam, the Netherlands.	2003-2006	100 (3.6)
Training 'SCID-1/P', Altrecht, Zeist, the Netherlands.	2004	8 (0.3)
1.3 In-depth courses		
Introduction in structural diagnostics, PDO-GGZ Leiden/Rotterdam, the Netherlands.	2003-2006	15 (0.5)
Complex diagnostics, PDO-GGZ Leiden/Rotterdam, the Netherlands.	2003-2006	45 (1.6)
Brain science, PDO-GGZ Leiden/Rotterdam, the Netherlands.	2003-2006	75 (2.7)
Psychiatric syndromes, PDO-GGZ Leiden/Rotterdam, the Netherlands.	2003-2006	90 (3.2)
Multicultural mental healthcare service, PDO-GGZ Leiden/Rotterdam, the Netherlands.	2003-2006	15 (0.5)
Principles of psychotherapy, PDO-GGZ Leiden/Rotterdam, the Netherlands.	2003	45 (1.6)
Psychodynamic theory and therapy, PDO-GGZ Leiden/Rotterdam, the Netherlands.	2003-2006	45 (1.6)
In-depth Cognitive Behavioral Therapy, PDO-GGZ Leiden/Rotterdam, the Netherlands.	2003-2006	45 (1.6)
Group psychotherapy, PDO-GGZ Leiden/Rotterdam, the Netherlands.	2003-2006	30 (1.1)
Family therapy, PDO-GGZ Leiden/Rotterdam, the Netherlands.	2003-2006	30 (1.1)
In-service training 'Short-term treatment in mental healthcare services', RINO Noord-Holland, Rotterdam, the Netherlands.	2009	16 (0.6)
In-service training 'Attachment, affect regulation and mentalization', Nederlands Psychoanalytisch Instituut (NPI), Vlaardingen, the Netherlands.	2010	16 (0.6)
Cognitive behavioral therapy in patients with physical symptoms, RINO Noord-Holland, Amsterdam, the Netherlands.	2011	18 (0.6)
1.4 Seminars and workshops		
Seminar 'Somatoform disorders: unexplained physical symptoms', Benecke, AMC, Amsterdam, the Netherlands.	2003	8 (0.3)
Seminar 'Psychosomatics and psychiatry: an intimate couple', Benecke, AMC, Amsterdam, the Netherlands.	2003	8 (0.3)

Workshop 'Cognitive behavioral therapy in somatizing patients', Cure & Care Development, Nijmegen, the Netherlands.	2004	8 (0.3)
Seminar 'Personality and psychopathology: treatment and etiology', Benecke, Maarssen, the Netherlands.	2008	8 (0.3)
Seminar 'Personality and psychopathology: setting and comorbidity', Benecke, Maarssen, the Netherlands.	2008	8 (0.3)
Lustrum seminar 'Couch, scan, talk and pills', Nederlands Instituut voor Psychologen (NIP), Haarlem, the Netherlands.	2008	8 (0.3)
Autumn conference 'Quite a character', Vereniging voor Gedragstherapie en Cognitieve therapie (VGCt), Veldhoven, the Netherlands.	2009	8 (0.3)
Seminar 'Treatment of insomnia', Bohn Stafleu van Loghum, Amersfoort, the Netherlands.	2010	8 (0.3)
Workshop Chris Iveson, Vereniging voor Gedragstherapie en Cognitieve therapie (VGCt), Utrecht, the Netherlands.	2010	8 (0.3)
Seminar 'Chronic fatigue syndrome', Vereniging voor Gedragstherapie en Cognitieve therapie (VGCt), Veldhoven, the Netherlands.	2010	8 (0.3)
Workshop 'Intensive and effective CBT for specific phobias: the one-session treatment', Vereniging voor Gedragstherapie en Cognitieve therapie (VGCt), Veldhoven, the Netherlands.	2011	8 (0.3)
National conference 'Unexplained Physical Symptoms 2011: body and mind: one management', Benecke, Barneveld, the Netherlands.	2011	8 (0.3)
Annual conference for clinical psychologists and clinical neuropsychologists 'The specialist online', Nederlands Instituut van Psychologen (NIP), Utrecht, the Netherlands.	2011	8 (0.3)
Two-days training 'Spinal Cord Stimulation for the treatment of Failed Back Surgery Syndrome', European Continuing Medical Training (ECMT), Zeist, the Netherlands.	2012	16 (0.6)
Annual conference for clinical psychologists and clinical neuropsychologists 'The DSM 5.0: source of inspiration and irritation', Nederlands Instituut van Psychologen (NIP), Utrecht, the Netherlands.	2012	8 (0.3)
Workshop 'Metacognitive therapy in generalized anxiety disorder', Vereniging voor Gedragstherapie en Cognitieve therapie (VGCt), Veldhoven, the Netherlands.	2012	8 (0.3)
Autumn conference 'Back to Basics?', Vereniging voor Gedragstherapie en Cognitieve therapie (VGCt), Veldhoven, the Netherlands.	2012	16 (0.6)
Conference 'Pain Days', Nederlandse Vereniging voor Anesthesiologie (NVA), Arnhem, the Netherlands.	2012	16 (0.6)
1.5 National conferences – participation and presentation		
Refresher course 'Coping with the consequences of medically unexplained physical symptoms', Bedrijfsgeneeskundige gezelschap Rijnmond, Vlaardingen, the Netherlands. Oral presentation: 'Unexplained physical symptoms'.	2006	4 (0.1)
Autumn conference 'Are you being served?', Vereniging voor Gedragstherapie en Cognitieve therapie (VGCt), Veldhoven, the Netherlands. Poster presentation: 'Re-examining Unexplained Physical Symptoms in primary care: working alliance and cognitive-behavioral group therapy'.	2008	16 (0.6)
Seminar 'Primary care: show yourself', Eerstelijns ondersteuning (ELO), Delft, the Netherlands. Poster presentation: 'Re-examining Unexplained Physical Symptoms in primary care: working alliance and cognitive-behavioral group therapy'.	2009	4 (0.1)
Refresher course 'Physical Unexplained Symptoms in broad perspective', Riagg Rijnmond, Vlaardingen, the Netherlands. Oral presentation; 'Physical Unexplained Symptoms through patients' eyes'.	2009	4 (0.1)
Autumn conference 'Change', Vereniging voor Gedragstherapie en Cognitieve therapie (VGCt), Veldhoven, the Netherlands. Oral presentation: 'Unexplained Physical Symptoms: change by linking to patients' perspective'.	2010	16 (0.6)

41th Lombardijen Forum 'Doctor, there must be something going wrong with me', Maasstad Ziekenhuis, Ridderkerk, the Netherlands. Oral presentation: 'Unexplained Physical Symptoms: change by linking to patients' perspective'.	2011	4 (0.1)
Conference 'Management of patients with unexplained physical symptoms', Leids Congres Bureau, Amsterdam, the Netherlands. Oral presentation: 'Unexplained Physical Symptoms: change by linking to patients' perspective'.	2011	8 (0.3)
Autumn conference 'Just do it?', Vereniging voor Gedragstherapie en Cognitieve therapie (VGCt), Veldhoven, the Netherlands. Poster presentation: 'Assess or just DO IT?'. Third prize for the best poster presentation.	2011	16 (0.6)
Meeting with Polikliniek Lichamelijk Onverklaarde Klachten VUmc en Polikliniek Psychosomatiek van GGZinGeest op Osdorpplein, Amsterdam, the Netherlands. Oral presentation: 'Unexplained Physical Symptoms: change by linking to patients' perspective'.	2012	2 (0.1)
1.6 Other		
Annual tutors' day - Post-master Education towards Healthcare Psychologist, PDO-GGZ Leiden/Rotterdam, the Netherlands.	2009	8 (0.3)
Annual tutors' day - Post-master Education towards Healthcare Psychologist, PDO-GGZ Leiden/Rotterdam, the Netherlands.	2010	8 (0.3)
2. Teaching	**Year**	**Contact hours (ECTS)**
2.1 Lecturing		
Teaching the 'SCID-I/P' to Aike van der Hoeven-Seubring, Carola Coolen, Jeanette den Dekker-Mast, Marloes Hilbers, Judith de Niet, Hanneke Buijks, Janine Blok en Ingrid Boden-van den Brand, psychologists with a Master's degree, Vlaardingen, the Netherlands.	2005-2006	8 (0.3)
Refresher course for general practitioners 'Unexplained Physical Symptoms', Department of General Practice of Erasmus MC, Rotterdam, the Netherlands.	2011	2 (0.1)
Optional Subject 'Unexplained Physical Symptoms: change by linking to patients' perspective' for students in their third curriculum year at the Faculty of Social Sciences of Erasmus University, Rotterdam, the Netherlands.	2011	1 (0.0)
Train the trainer in the group training 'Coping with the consequences of Unexplained Physical Symptoms' for Healthcare Psychologists, psychotherapists and clinical psychologists at the Department of Anesthesiology of Academic Medical Center (AMC)/University of Amsterdam, Amsterdam, the Netherlands.	2011-2012	18 (0.6)
Optional Subject 'Unexplained Physical Symptoms: change by linking to patients' perspective' for students in their third curriculum year at the Faculty of Social Sciences of Erasmus University Rotterdam, the Netherlands.	2012	1 (0.0)
2.2 Supervisor of post-master students		
Supervisor in psychodiagnostics for Patricia Vos, Maricia de Koning, Astrid van Jaarsveld, students of the Post-master Education towards Healthcare Psychologist, PDO-GGZ Leiden/Rotterdam, the Netherlands.	2005-2006	60 (2.1)
Supervisor in psychodiagnostics for Astrid van Jaarsveld, Mechteld Graafmans, students of Post-master Education towards Healthcare Psychologist, PDO-GGZ Leiden/Rotterdam, the Netherlands.	2006-2007	40 (1.4)
Supervisor in psychodiagnostics for Lieke Kraut, student of the Post-master Education towards Healthcare Psychologist, PDO-GGZ Leiden/Rotterdam, the Netherlands.	2007-2009	80 (2.9)
Supervisor in psychodiagnostics for Ulas Cardakli, student of the Post-master Education towards Healthcare Psychologist, PDO-GGZ Leiden/Rotterdam, the Netherlands.	2009	14 (0.5)
2.3 Other		
Tutor of the students of GZ09P following the Post-master Education towards Healthcare Psychologist, PDO-GGZ Leiden/Rotterdam, the Netherlands.	2009-2011	41 (1.5)

One ECTS (European Credit Transfer System) equals a study workload of 28 hours.
Contact hours are the working hours without preparation.

Publications



Publications

1. Zonneveld LNL, McGrath PJ, Reid GJ, Sorbi MJ. Accuracy of children's pain memories. Pain 1997;71(3):297-302.

2. Zonneveld LNL. Draaiboek (trainers) 'Omgaan met de gevolgen van onverklaarde lichamelijke klachten'. Vlaardingen/Rotterdam: Riagg Rijnmond/Erasmus MC Afdeling Medische Psychologie en Psychotherapie, 2005.

3. Zonneveld LNL. Werkboek (patiënten) 'Omgaan met de gevolgen van onverklaarde lichamelijke klachten'. Vlaardingen/Rotterdam: Riagg Rijnmond/Erasmus MC Afdeling Medische Psychologie en Psychotherapie, 2005.

4. Zonneveld LNL, Van 't Spijker A, Passchier J, Van Busschbach JJ, Duivenvoorden HJ. The effectiveness of a training for patients with unexplained physical symptoms: protocol of a cognitive behavioral group training and randomized controlled trial. BMC Public Health 2009;9:251.

5. Zonneveld LNL, Duivenvoorden HJ, Passchier J, Van 't Spijker A. Tailoring a cognitive behavioural model for unexplained physical symptoms to patient's perspective: a bottom-up approach. Clinical Psychology and Psychotherapy 2010;17(6):528-535.

6. Zonneveld LNL, Van 't Spijker A, Van Busschbach JJ. Bevorderen van gepaste zorg voor patiënten met onverklaarde lichamelijke klachten: een voorbeeld. GZ-psychologie 2012;4(2):10-15.

7. Zonneveld LNL, Van Rood YR, Timman R, Kooiman CG, Van 't Spijker A, Busschbach JJV. Effective group training for patients with unexplained physical symptoms: a randomized controlled trial with a non-randomized one-year follow-up. PLoS ONE 2012;7(8):e42629.

8. Zonneveld LNL, Van Rood YR, Kooiman CG, Timman R, Van 't Spijker A, Busschbach JJV. Predicting the outcome of a cognitive-behavioral group training for patients with unexplained physical symptoms: a one-year follow-up study. BMC Public Health 2012;12:848.

9. Zonneveld LNL, Sprangers MAG, Kooiman CG, Van 't Spijker A, Busschbach JJV. Patients with unexplained physical symptoms have poorer quality of life and higher costs than other patient groups: a cross-sectional study on burden. 2012:submitted.

10. Visser MS, Zonneveld LNL, Van 't Spijker A, Busschbach JJV. The cost-effectiveness of cognitive-behavioral group training for unexplained physical symptoms. 2013:submitted.

www.onverklaarde-klachten.nl