Psychological Aspects in Rehabilitation

A wide view expands the mind

Ernst Schrier

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rijksuniversiteit
groningen

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Proefschrift

ter verkrijging van de graad van doctor aan de
Rijksuniversiteit Groningen
op gezag van de
rector magnificus prof. dr. E. Sterken
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

woensdag 19 juni 2019 om 16.15 uur

door

Ernst Schrier

geboren op 28 april 1953
te Utrecht

Promotores

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The publication of this thesis is financially supported by:

Rijksuniversiteit Groningen
University Medical Center Groningen, Centrum voor Revalidatie.
Research institute SHARE

Stichting Beatrixoord Noord Nederland

Cover design: A Wide View, Hanneke Graatsma
Cover and layout design: Graatsma & Schrier
Printed by: GVO drukkers & vormgevers B.V.

Ernst Schrier: Psychological Aspects in Rehabilitation, a wide view expands the mind.
Thesis University of Groningen, the Netherlands.

ISBN: 978-94-034-1754-7
ISBN: 978-94-034-1753-0 (e-book)

CONTENTS

Chapter 1

General introduction

People consider their health to be very important.[1] In the Netherlands, yearly more than 10% of the Gross Domestic Product is being spent on health.[2] But what does health actually mean? The World Health Organization (WHO) defined health in its 1948 Constitution as "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity". This definition is still standing today, although under discussion, particularly regarding the phrase "absence of disease".[3] With optimism after the second world war and introduction of better hygiene and antibiotics, the WHO assumed that diseases could be eradicated. Today, more than 70 years later, diseases are part of our life. Where some diseases have been eradicated, others became chronic. People suffer increasingly from chronic diseases and have to find ways to adapt to them.[4] Another change in this period is the physician-patient working alliance. Traditionally the biomedical model was applied. The biomedical model assumed that all disease processes could be completely explained by an underlying biological mechanism. The physician was the authority and decided what to do. Today more and more health consumers are expecting to be heard, understood and respected, and want to be involved in decision making.[5] In the Netherlands a discussion about the WHO definition of health was initiated in 2009 by the health counsel for the Netherlands, an independent scientific advisory body for government and parliament. After an international conference: Is health a state or an ability? Replacement of the WHO definition of health was supported and a new concept was formulated. This concept for a new health definition was published in 2014.[6] The new proposal on health definition states "the ability of individuals or communities to adapt and self-manage when facing physical, mental or social changes".[6] Within this definition, the still habitually used biomedical model is too restricted, the biopsychosocial model fits better.

The biopsychosocial model was presented by Engel in November 1977 at the 23rd Cartwright Lecture at the Columbia University College of Physicians and Surgeons, under the title, "The Biomedical Model: A Procrustean Bed?" In the biopsychosocial model it is critical to merge the psychological and social dimension with the physical dimension when studying and treating diseases.

Beside the integration between mind and body the patient should be seen as his/her manager. The patient manages (part of) his/her own care.[7]

The new vision on health and the biopsychosocial model is used in rehabilitation medicine. Rehabilitation medicine is specialized in adapting to the consequences of adversity caused by e.g. disease or trauma, such as reduction of functioning or activities and decreased participation in work, leisure or social life. The main purpose of rehabilitation medicine is to support the patient on optimal functioning in society and restore all domains of quality of life (QOL).[8,9] All professionals of the rehabilitation team support the patient in the effort to reach an optimal QOL. Psychological treatment in rehabilitation focuses on the patients acceptance of and adaption to consequences or restrictions of a disease. Is the patient able to return to his/her previous QOL, within the restrictions and with the consequences, caused by the adversity? Or is the patient developing dysfunctional cognitions, mood or anxiety

problems and experiencing a decreased QOL. Through various types of treatments, by applying for instance Cognitive Behavioral Therapy, Solution Focused Therapy or Acceptance and Commitment Therapy, the psychologist is helping the patient to accept and adapt to restrictions or consequences of adversity. The results of those treatments with regard to the mentioned goal are positive, sometimes promising but not always conclusive.[10-14]

Psychological factors, such as cognition or resilience, alter the impact of a disease. But psychological factors are also linked to a situation or a context. For instance, a patient moves generally fearless, while at the same time he is afraid to move the right hand. There are strict factors, like optimism and there are broad factors, for instance resilience, containing strict factors as optimism and hardiness. Where some factors are more trait (personality) thus more stable, others are more state (anxiety), thus dynamic.

There is a lack of knowledge of the association of psychological factors and the QOL of patients with a disease, especially the causal relationship.[15-18] In daily practice, we want to know more about that relationship to reveal psychological factors for the patient to change or for the therapist to treat or to predict the outcome of the rehabilitation.

A case from my own daily practice clarifies questions that can arise from a referral.

I just started working as a psychologist in the outpatient clinic of the Department of Rehabilitation Medicine at the University Medical Center in Groningen when I received the following referral: "Is the proposed amputation for this patient, a 45 year old man with Complex Regional Pain Syndrome type I (CRPS-I), the right decision?" I had absolutely no idea what to advice, even the reasoning behind the question confused me. Was the implicit question of the rehabilitation physician: "has this patient a psychiatric disorder?" And are there psychiatric disorders that contra indicate an amputation e.g. conversion? Was there any doubt about the patients considerations (his ability to make any decision) concerning this request of amputation? Were there psychological factors influencing the beginning or maintenance of the CPRS-I and was I supposed to reveal them? During my first assessment the request of the patient's was crystal clear: "Please amputate that thing!" How should I weigh this request? According to the Dutch CRPS-I guidelines: There is insufficient evidence that amputation positively contributes to the treatment of CRPS-I?[19] Has the patient weighed the decision sufficiently? I am unknown with any cutoff score regarding that decision process. What was the goal behind patient's request to get rid of "that thing" to acquire a better life or QOL? To experience less pain? Within one hour I had so many questions but all with more or less the same background: how is psychology fitting into this biopsychosocial model? What is the connection between the physical and the psychosocial domains of the biopsychosocial model. These questions were good motivators for research. In this patient with CRPS-I, who wanted less pain and gain mobility in order to increase his QOL, are psychological factors associated with those particular outcomes? Can we specify that association and might we even predict part of the outcome?

Sequel in discussion (page 134)

Now, many years later, some of the answers I was looking for are gathered and presented in this thesis.

To measure the impact of a disease on QOL and acquire norm scores for QOL of rehabilitation outpatients, measurement of QOL was initiated. The World Health Organization Quality of Life questionnaire (WHOQOL-bref) was used to measure QOL. It is an international instrument for measuring QOL in 4 domains: physical, psychological, social and environmental and these 4 domains fit the biopsychosocial model.[20] Because no QOL values for rehabilitation outpatients were known, the first study was devoted to explore QOL in rehabilitation outpatients. The results of that study are presented in *chapter 2*.

Thereafter the focus of research shifted from QOL to cognition because cognitive dysfunction e.g. lack of concentration, poor memory, disturbed executive functions were brought up by rehabilitation patients as an obstacle in their daily life. These clinical findings were remarkable because none of these outpatients had brain damage. This type of cognitive dysfunction was not reported in rehabilitation outpatients, without brain damage, before. In previous research associations of e.g. gender, age, diagnosis, recent surgery and pain with cognitive failure had been reported.

For rehabilitation outpatients the occurrence of cognitive problems and which factors might be associated with the cognitive problems was unknown. In *chapter 3,* a study, in 274 rehabilitation outpatients, is presented assessing cognitive failure and possible associations with gender, age, diagnosis, recent surgery, pain and stress coping ability.

Another research question originated from daily practice around lower limb prosthesis. In the fitting process of a prosthesis in the case of a trans tibial amputation some patients were not satisfied. In *chapter 4* a systematic review is presented regarding factors influencing satisfaction with the prosthesis, including psychological factors. The factors reported in literature were classified in 5 domains: appearance, properties, fit, and use of the prosthesis, as well as aspects of the residual limb.

In *chapter 5, 6 and 7* studies are presented about patients who underwent an amputation for chronic therapy resistant CRPS-I, a rare condition with a normally favorable prognosis. In some cases, the CRPS-I is therapy resistant. All participants of the research in *chapter 5, 6 and 7* suffered from this syndrome and underwent an amputation in attempt to reduce pain, increase mobility and increase QOL. Because the outcomes of the first 22 patients, amputated between May 2000 to October 2008, exceeded expectations of the research team, the question arose why these patients did rather well.[21] High resilience could be an explanation for these unexpected results and it became therefor the topic of research. Resilience was first described in children.[22] Children with severe adversity in their youth did relatively well and therapists wondered why. It was discovered that children with high resilience or stress coping ability did better than those with poorer resilience.[23] It was not clear however, if QOL, the post amputation outcome measurement in the case of therapy resistant CRPS-I, was associated with resilience. In *chapter 5*, a

study is presented about the association between resilience and QOL in the above mentioned patients.
Because resilience is only one factor and the study in *chapter 5* was cross sectional, the research was extended to more factors and a longitudinal design. In 31 participants, amputated for long standing therapy resistant CRPS-I, psychological factors, measured before and after the amputation, were analyzed. In *chapter 6*, results of that longitudinal study are presented.
Besides resilience, QOL, depression, anxiety, psychological distress, childhood adversity, life events, psychiatric (DSM-IV) history or psychiatric disorder, lawsuit, and social support were analyzed. In *chapter 7* a study is presented of long term outcome of all patients, amputated in the last 17 years, 48 patients participated. Of 19 participants we were able to compare their outcomes with outcomes of 7 years ago.
In *chapter 8* the decision making process to amputate or not is presented as it is currently applied. That chapter is an invitation for an international discussion about amputation in case of longstanding therapy resistant CRPS-I. Because amputation in case of longstanding therapy resistant CRPS-I is rare and the patients are determined to have an amputation performed, a (randomized) controlled trial is almost impossible to perform. By publishing our decision making process we hope to contribute to an international discussion regarding this topic.

Outline of the thesis

Chapter 2
-QOL study-
QOL in rehabilitation outpatients: normal values and a comparison with the general Dutch population and psychiatric patients.
Research question: What are the Dutch norm values of QOL for rehabilitation outpatients of the World Health Organization Quality of Life questionnaire (WHOQOL-BREF) and what is the association of diagnosis and patient characteristics with those values?

Chapter 3
-Cognitive dysfunction study-
Subjective cognitive dysfunction in rehabilitation outpatients with musculoskeletal disorders or chronic pain.
Research question: What is the magnitude of cognitive dysfunction in rehabilitation outpatients and is cognitive dysfunction associated with patient characteristics, diagnosis, surgery, pain, anxiety, stress and depression?

Chapter 4
-Prosthesis satisfaction review-
Prosthesis satisfaction in lower limb amputee: a systematic review of associated factors and questionnaires.
Research question: Which factors are influencing the transtibial prosthesis fit and how is satisfaction operationalized in the different questionnaires?

Chapter 5
-Resilience in CRPS-I study-
Resilience in patients with amputation because of CRPS-I.
Research question: What is the association between resilience and post amputation outcomes, i.e. QOL, pain, recurrence of CRPS-I and psychological distress?

Chapter 6
-Association with outcome study-
Psychosocial factors associated with poor outcomes after amputation for CRPS-I.
Research question: Which psychosocial factors assessed prior to amputation are associated with poor outcomes of amputation for longstanding therapy resistant CRPS-I?

Chapter 7
-Outcome study-
Outcomes of amputation because of longstanding therapy-resistant CRPS-I
Research question: What are the long-term outcomes of amputation in patients with longstanding and therapy-resistant CRPS-I, regarding QOL, pain, recurrence of CRPS-I, use of a prosthesis and functioning in daily life?

Chapter 8
-Decision paper-
Decision making process for amputation in case of therapy resistant CRPS-I
Research question: What is the current state of the decision making process for amputation in longstanding therapy resistant CRPS-I in the UMCG, the Netherlands?

Chapter 9
-General discussion-

Summary

Samenvatting

Dankwoord

Chapter 2

Quality of life in rehabilitation outpatients: normal values and a comparison with the general Dutch population and psychiatric patients

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Qual Life Res. 2016 Jan;25(1):135-142

Abstract

Purpose: Provide Dutch normal values for rehabilitation outpatients with chronic pain or musculoskeletal diseases utilizing the World Health Organization Quality of Life questionnaire abbreviated version (WHOQOL-BREF) and analyse influence of diagnosis and patient characteristics on normal values and increase understanding in those values.
Methods: 542 outpatients, referred to a rehabilitation psychologist. Referral diagnoses were "musculoskeletal", "chronic pain", "neurological" and "miscellaneous". Comparisons between groups were made for each of the four domains of the WHOQOL-BREF (scoring range 4-20).
Results: Domain scores of rehabilitation outpatients were: physical domain, 11.0 (±2.7), psychological domain 13.6 (±2.4), social domain 14.8 (±3.4) and environmental domain 14.2 (±2.2). Outpatients with chronic pain reported the lowest scores on the WHOQOL-BREF when compared to the "musculoskeletal", "neurological" and "miscellaneous" groups. Increased age, lower education, living alone and unemployment had a negative impact on WHOQOL-BREF scores. Compared to the general Dutch population, rehabilitation outpatients scored, unadjusted for age, significantly lower (difference for the physical domain 4.5 (95% confidence interval (CI): 4.2; 4.8), the environment domain 1.7 (95% CI: 1.5; 2.0), the psychological domain 1.1 (95% CI: 0.4; 1.2) and the social domain 0.4 (95% CI: 0.0; 0.8).
Conclusions: WHOQOL-BREF scores of rehabilitation outpatients are lower and differed significantly from normal values of a Dutch population in all four domains. Therefore the WHOQOL-BREF can be used to measure the subjective impact of their disease or injury. The subjective impact of chronic pain was found to be particularly high.

Introduction

Due to modern health care more and more patients with potentially lethal diseases are cured or disease progression is reduced [1]. Therefore, the treatment goals of patients in rehabilitation have shifted from how to survive into how to adapt to and cope with a chronic disease [2]. In the last decades, the patient's perspective on the pros and cons of treatment has grown in importance, resulting in increased attention for the impact of (chronic) disease or injury on patient's quality of life (QOL). QOL can be assessed utilizing the WHOQOL-BREF [3], in which QOL is defined as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns". Domain scores are scaled in a positive direction (i.e. higher scores denote higher QOL).
It should be noted that apart from disease and injury, QOL is also influenced by social functioning [4, 5], education, employment [6], comorbidity [7], self-efficacy [8], and goal adjustment [9]. Furthermore, both gender and age influence QOL;

women score significantly higher on the social domain of QOL and lower on all the other domains of QOL compared to men [10]. Finally, QOL has been shown to decrease with increasing age [11]. A decreased QOL is found in patients with a somatic disease as well as in patients with a psychiatric disorder [4, 12-14]. In the latter case, QOL is inversely related to severity of psychopathology [4, 7].
The negative influence on the QOL by somatic and psychiatric diseases is found in all domains. This influence is well understood since Engel introduced the biopsychosocial model [15]. This model is the foundation of the multidisciplinary treatment approach in rehabilitation. Today the International Classification of Functioning (ICF) is adopted as a framework for rehabilitation and an important goal in rehabilitation is to increase QOL of patients [16, 17]. Currently no normal values for QOL of Dutch rehabilitation outpatients are available, which are essential for a correct comparison between rehabilitation outpatients, the general Dutch population and psychiatric outpatients. Normal values for rehabilitation outpatients provide insight into whether the instrument can measure the impact and variations of a disease or injury on the QOL.
The aims of this study were to provide normal values for Dutch rehabilitation outpatients with chronic pain or musculoskeletal diseases utilizing the WHOQOL-BREF, to analyse the influence of diagnosis and patient characteristics of rehabilitation outpatients on normal values and to compare normal values with those of the general Dutch population and psychiatric outpatients.

Method

Patients
Between January 2008 and January 2013, 607 outpatients from the Department of Rehabilitation Medicine of the University Medical Centre Groningen (UMCG) were referred to a psychologist. They were referred by a rehabilitation specialist for a psychological assessment and/or treatment. Prior to this assessment, a set of questionnaires and a consent form were sent by mail to the patients with a request to fill out all forms. During the assessment a semi-structured interview was conducted to determine a treatment plan. During the intake procedure, patient's gender, age, educational level, employment, and marital status were collected. The rehabilitation specialist's referral medical diagnosis was retrieved from the medical records.
Reference groups
The general Dutch population reference group was based on the Dutch manual WHOQOL-100 and WHOQOL-BREF. This group of 626 persons had a mean age of 53.9 (SD 16.2) and 67.5% of the group were women [18].
The psychiatric reference group consisted of 410 psychiatric outpatients with a mean age of 33.5 (SD 8.3) and 58.8% of the group were women. It was a mixed diagnostic group: 54 persons who did not obtain a DSM-IV diagnosis, 224 with a single axis diagnosis and 132 with a diagnosis on axis 1 as well as axis 2 [7].
Instruments
The WHOQOL-BREF is a condensed version of the WHOQOL questionnaire. The WHOQOL-BREF is a 26 item questionnaire that correlates well with the original 100

item questionnaire (r ranges between 0.88 and 0.96) [19]. It assesses the individual's perceptions in the context of his/her culture and value system, personal goals, standards and concerns. The WHOQOL instruments were developed collaboratively in a number of centres worldwide, and have been field-tested widely [20]. Of the 26 items, 24 items were used to calculate the 4 QOL domains; physical health (7 items), psychological (6 items), social relationships (3 items) and environment (8 items). Transformed domain scores range from 4 to 20. A higher score indicates a better QOL. The two remaining items, sometimes used to calculate overall QOL and health, were not used in this study as recommended by the WHO.

Analysis

Data was anonymised and analysed using IBM SPSS Statistics (v.20). P-P and Q-Q plots were used to assess the normal distribution of the dependent variables. Results are significant at $p \leq 0.05$ unless stated otherwise. A Pearson Chi-Square test and ANOVA were used to determine whether gender, marital status, education, employment and age differed between the referral diagnosis groups. The dependent variables in the current study were the scores on the four domains of the WHOQOL-BREF. The WHOQOL-BREF scores of the referral diagnosis groups were compared using a one way ANOVA. A series of Tukey's post-hoc tests were used for pair-wise comparisons. For regression analyses several dummy variables were computed. Education was dichotomized into low education (1 = low and lowest, 0 = middle and high) according to the International Standard Classification of Education (ISCED) 2011. Low education equals the ISCED level 0-4, middle the level 5 and high the level 6-9 [21]. Social status was dichotomized into living alone (0 = living alone, 1 = living with the family or a partner), referral diagnosis was dichotomized into chronic pain (1 = chronic pain, 0 = musculoskeletal, neurological and miscellaneous) and employment was dichotomized in employment (0= retired, unemployed, student, welfare, 1 = work, sick leave compensation). In the Dutch society persons who are on sick leave keep their job for at least two years and get between 70 and 100% financial compensation, and for this reason sick leave compensation was counted as work. To analyse the influence of gender, age, education, social status, employment and diagnosis, a hierarchical step wise regression analysis was applied for each domain of WHOQOL-BREF. To compare differences in means of rehabilitation outpatients with a general Dutch population and psychiatric outpatients [4], confidence intervals (CI) for differences in means were calculated for each domain, unadjusted for age and or gender, since data on a personal level of the reference groups were not available [22].

Results

In total, 65 patients were excluded from the current study (11%); 32 did not sign informed consent, 18 were under 18 years of age and 15 were excluded because of missing data resulting in 542 potential participants in the current study.

Four referral diagnosis groups were specified, based on the diagnosis treatment combination used in the Netherlands to categorize patients for funding purposes, this method is used in all Dutch rehabilitation centers.
The first referral diagnosis group was "musculoskeletal" including "disease or injury of the upper extremity" and "other musculoskeletal diseases" (n=280, 52%). The second referral diagnosis group was "chronic pain" including patients with chronic pain (n=174, 32%). The third referral diagnosis group was "neurological" including "diseases or injury of the central nerve system" or "peripheral nerves" (n=59, 11%) and the last group is a miscellaneous group (n=29, 5%) (Table 1).

Table 1 Referral diagnosis of the rehabilitation specialist and grouping of patients in the current study.

Diagnosis	**Division of the groups**	**n**
Musculoskeletal diseases	Musculoskeletal	280
Chronic pain	Chronic pain	174
Neurology	Neurological	59
Brain injury	Miscellaneous	7
Paraplegic	Miscellaneous	2
Amputations	Miscellaneous	16
Organs	Miscellaneous	4
Total		542

A benchmark was made in 2012 of all treatments (n=103410) in 20 Dutch rehabilitation centers, according to the same categories. Brain injury patients were the largest group (32%) followed by musculoskeletal (24%), chronic pain (17%), neurology (13%), organs (6%), paraplegic (5%) and amputations (3%) in that benchmark [23]. In our study in outpatients brain injury was rare but the other three most important diagnosis groups had a similar distribution. Because the same method to diagnose was used we expect that our sample is representative for at least musculoskeletal group and chronic pain group. In total, 68% of the patients were female; 88% had an age between 20 and 60 years. A majority of patients were living with a partner (67%), 11% lived with their parents, 22% lived alone and 56% were employed (Table 2).
Gender (χ^2 (df 3, n= 542) = 4,197, p= .241), marital status (χ^2 (df 6, n= 542) = 7.088, p= .313), education (χ^2 (df 6, n= 542) = 4,144, p= .657) and employment (χ^2 (df 3, n= 542) = 7,755, p= .051) did not differ significantly between the different diagnosis groups. Employment was almost a significant difference between groups, most deviant were the neurological group and the miscellaneous group. The four domains of the QOL were normally distributed. Chronbach's alpha for the WHOQOL-BREF was .90. Removing items from the questionnaire resulted in lower values of alpha.

Table 2 Characteristics of participants and according to referral diagnosis of the rehabilitation specialist.

	Total group (n=542)	**Musculo-skeletal (n= 280)**	**Chronic pain (n= 174)**	**Neurological (n=59)**	**Miscellaneous (n=29)**	**P value**
	n (%)	n (%)	n (%)	n (%)	n(%)	
Female	366 (67.5%)	196 (70.0%)	116(66.6%)	39(66.1%)	15(51.7%)	0.241a
Education						0.313a
--Low/ lowest	198(36.5%)	97 (34.6%)	73(42.0%)	20(33.9%)	8(27.6%)	
--Medium	211 (38.9%)	113 (40.4%)	63(36.2%)	23(39%)	12(41.4%)	
--High	133 (24.6%)	70 (25.0%)	38(21.8%)	16(27.1%)	9(31%)	
Social status						0.657a
--Alone	121(22.3%)	57 (20.4%)	41(23.6%)	12(20.3%)	11(37.9%)	
--With parents	58 (10.7%)	31 (11.0%)	17(9.8%)	9(15.3%)	1(3.4%)	
-- With partner	363 (67.0%)	192 (68.6%)	116(66.6%)	38(64.4%)	17(58.6%)	
Employed	302(55.7%)	168(60.0%)	96(55.2%)	25(42.4%)	13(44.8%)	0.051a
Age, mean (sd)	41.0 (14.0)	40.3 (14.2)	41.7 (14.0)	41.8 (12.8)	43.7(15.6)	0.491b

a: chi square test, b: ANOVA

Compared to the total group rehabilitation outpatients, the chronic pain group scored significantly lower in every domain except the environment, the musculoskeletal group scored significant higher in all four domains. There is a significantly difference between the musculoskeletal group and the chronic pain group in all four domains. (Table3).

Table 3 Comparison of WHOQOL-BREF domains between the four diagnosis groups of rehabilitation outpatients included in the University Medical Centre Groningen between 2008 and 2012.

Domain	**Total group outpatients n = 542 Mean (SD)**	**Musculo-skeletal n = 280 Mean (SD)**	**Chronic pain n = 174 Mean (SD)**	**Neurological n = 59 Mean (SD)**	**Miscellaneous n=29 Mean(SD)**	**One-way between groups ANOVA p value**
Physical	11.0(2.7)	11.4(2.5)	10.1(2.6)	10.6(3.0)	12.0(2.9)	0.001[a]
Psychological	13.6(2.4)	14.0(2.3)	13.1(2.4)	13.8(2.5)	13.5(2.6)	0.001[a]
Social	14.8(3.4)	15.3(3.2)	14.1(3.4)	14.5(3.8)	14.4(3.8)	0.004[a]
Environment	14.2(2.2)	14.5(2.1)	13.9(2.3)	14.0(2.2)	14.3(2.2)	0.025[a]

a: The p-value concerns the main effect of the ANOVA, post hoc Tukey test showed a significant difference between the chronic pain diagnosis group and musculoskeletal diagnosis group in all domains and between the chronic pain diagnosis and the miscellaneous in the physical domain.

The results of the regression analyses are summarized in Table 4.

Table 4 Results of the stepwaise regression analyses with the different domains of the WHOQOL-BREF as dependent variables rehabilitation outpatients (n=542).

	B	SE B	Sig	95% Confidence interval	
Physical domain					
Step 1	-0.025	0.008	0.003	-0.041	-0.008
Gender/male	0.367	0.249	0.141	-0.122	0.857
Education/low	-0.674	0.241	0.005	-1.147	-0.200
Living together	0.172	0.279	0.539	-0.376	0.719
Employed	0.408	0.236	0.084	-0.055	0.871
Step 2					
Chronic pain	-1.123	0.241	<0.001	-1.599	-0.653
Psychological domain					
Step 1					
Age	-0.015	0.008	0.056	-0.029	0.000
Gender/male	-0.140	0.225	0.535	-0.582	0.302
Education/low	-0.339	0.218	0.120	-0.766	0.089
Living together	0.760	0.252	0.003	0.265	1.255
Employed	0.636	0.213	0.003	0.218	1.054
Step 2					
Chronic pain	-0.788	0.219	<0.001	-1.219	-0.358
Social domain					
Step 1					
Age	-0.042	0.011	<0.001	-0.063	-0.021
Gender/male	-0.385	0.314	0.221	-1.002	0.232
Education/low	-0.350	0.304	0.250	-0.947	0.247
Living together	0.530	0.351	0.132	-0.161	1.220
Employed	0.997	0.297	0.001	0.413	1.580
Step 2					
Chronic pain	-0.916	0.307	0.003	-1.519	-0.312
Environment domain					
Step 1					
Age	-0.016	0.007	0.014	-0.029	-0.003
Gender/male	0.194	0.198	0.327	-0.195	0.583
Education/low	-0.945	0.191	<0.001	-1.321	-0.569
Living together	0.485	0.221	0.029	0.051	0.920
Employed	0.489	0.187	0.009	0.121	0.856
Step 2					
Chronic pain	-0.443	0.194	0.023	-0.825	-0.062

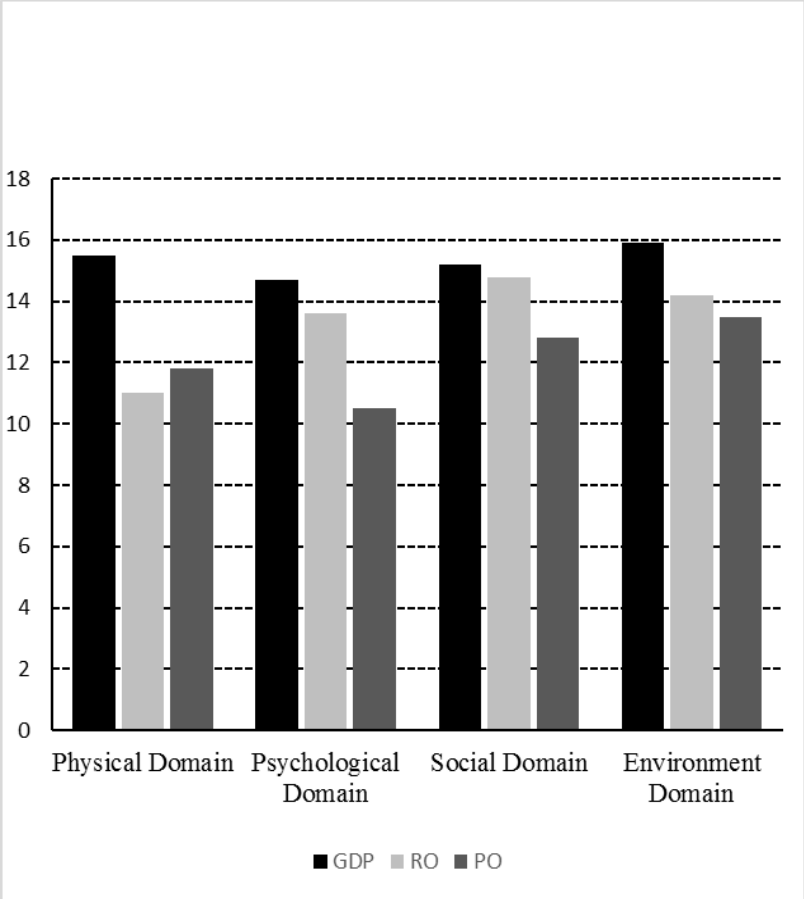
For gender the reference group was female, for education the reference group was middle or high education, for living together (consists of living with the family or a partner) the reference group was living alone, for employed the reference group was unemployment and for chronic pain the reference group was the other diagnosis groups (musculoskeletal, neurological and miscellaneous).

Tabel 5 Comparison of domains of WHOQOL-BREF between the general Dutch population, rehabilitation outpatients seen in University Medical Center Groningen between 2008 and 2012, and the psychiatric outpatients (not adjusted for age and gender).

	General Dutch population (n=626[a])					**Rehabilitation outpatients (n=542)**					**Psychiatric outpatients (n=410)**	
Domain	**Mean**	**sd**	**Dif[c]**	**95% CI[b] lower**	**95% CI upper**	**Mean**	**sd**	**Dif**	**95% CI lower**	**95% CI upper**	**Mean**	**sd**
Physical	15.5	2.7	4.5	4.2	4.8	11.0	2.7	0.8	0.4	1.2	11.8	3.0
Psycho-logical	14.7	2.2	1.1	0.4	1.2	13.6	2.4	-3.1	-3.4	-2.8	10.5	2.5
Social	15.2	2.9	0.4	0.0	0.8	14.8	3.4	-2.0	-2.4	-1.6	12.8	3.5
Environ-ment	15.9	2.2	1.7	1.5	2.0	14.2	2.2	-0.7	-1.0	-0.4	13.5	2.5

a: owing to missing data the number of participants from the general Dutch population differ per domain (range 619-626).
b: Confidence interval. c: Difference

Figure 1 Comparison of domains of WHOQOL-BREF between the general Dutch population (GDP), rehabilitation outpatients (RO) included in the University Medical Center Groningen between 2008 and 2012, and the psychiatric outpatients (PO) (not adjusted for age and gender).



Discussion

The current study aimed to provide normal values of the WHOQOL-BREF for outpatients in rehabilitation, and to gain insight into the influence of diagnosis and patient characteristics on QOL. Compared to the general Dutch population, rehabilitation outpatients scored, lower on all domains of WHOQOL-BREF; the physical domain most strongly. A higher age had a negative impact on QOL in all domains except the psychological domain. Unemployment had a negative impact on all domains except the physical domain. Living alone influenced the psychological and environmental domains negatively. Lower education influenced the physical and environmental domains negatively. Finally, gender had no significant influence on any domain.

Diagnosis

In all four domains, the patients suffering from chronic pain were found to have a lower QOL than the musculoskeletal group. This influence was also significant after correcting for patient characteristics in all domains of WHOQOL-BREF. This finding

corresponds with the concept that the emotional component plays an important role in chronic pain [24, 25].

Rehabilitation patients, psychiatric patients and general Dutch population compared

Both psychiatric outpatients and rehabilitation outpatients scored lower on the physical domain than the general Dutch population, with the rehabilitation patients scoring the lowest. The psychiatric patients scored lower in the other three domains compared to the general Dutch population and to the rehabilitation outpatients. Further analyses revealed that the chronic pain patients had a lower score on the psychological domain but not as low as the psychiatric patients. The comparison with the psychiatric patients was not adjusted for age and gender. The comparison with the general Dutch population was not adjusted for age because data to do so were not available. Some age differences were present in our study. The mean age of the general Dutch population was 53.9 (SD 16.2), of the rehabilitation outpatients 41.0 (SD 14.0) and of the psychiatric outpatients 33.5 (SD 8.3). In a large WHOQOL-BREF study in the UK (n = 4628), including healthy people and people suffering from different health conditions, effects of age on WHOQOL-BREF scores was small. [26]. There were no gender difference between the general Dutch population and the rehabilitation outpatients. These findings validate the assumption that rehabilitation patients primarily show difficulties coping with their physical problem and psychiatric patients with their mental problems.

QOL as outcome measure / Implications

The ability of the WHOQOL-BREF to evaluate change over time was investigated in a study within an outpatient rehabilitation setting. That study concluded that the questionnaire was a useful instrument for outcome measurement [17]. Also, statistical significant differences were found in all but the social domain, using raw data, between admission and discharge. Because raw data was used it is difficult to assess the clinical impact of these differences. Moreover, the study used a small sample of 55 patients. WHOQOL –BREF has been used as a routine outcome measure and changes were found in pre-post scores for some of 13 interventions investigated [26]. Only three of the interventions found a significant response in three or more domains: treatment as usual for depression, treatment as usual for arthritis and massage for chronic pain. Only four of the 13 treatments reported improvement in the psychological domain. The conclusion was that the responsiveness of the WHOQOL-BREF is limited or that the interventions were ineffective [26].

In the current study QOL was measured once. The largest difference between the general Dutch population and the rehabilitation outpatients was in the physical domain, approximately 4 points on a 4 to 20 scale. The difference between the general Dutch population and rehabilitation outpatients was 1.1 point on the psychological domain and only 0.4 on the social domain. In our opinion the differences in the psychological and social domain are small. This finding upholds one of the conclusions of the aforementioned study, of a limited responsiveness [26].

Strengths and limitations

The strength of the current study is the number of consecutive participants over a five year period. All referred patients were asked to participate. Of these participants, only 11% were excluded. Limitation of the current study is a missing

base-line measurement of QOL before the trauma or disease. However these data cannot be obtained.

Conclusion

In rehabilitation outpatients, scores on all WHOQOL-BREF domains were significant lower than those of the general Dutch population. Therefore the WHOQOL-BREF can be used to measure the subjective impact of their disease or injury in rehabilitation outpatients. A small but significant negative effect of increased age and unemployment was found on three domains, of living alone on two domains, and of lower education also on two domains of QOL.

Patients with chronic pain were found to exhibit a significant lower QOL in all four domains when compared to the group of patients with musculoskeletal problems. The differences between the rehabilitation outpatients and the general Dutch population on the psychological and social domain are small.

Conflict of interest

The authors declare no conflict of interest.

Statement of human rights

This project is assessed by the Medical ethics Review Board and they state that it fulfils all the requirements of our University Hospital for publication of patient data.

Informed consent

Informed consent was obtained from all individual participants included in the study.

References

1. Ory MG, Ahn S, Jiang L, Smith ML, Ritter PL, Whitelaw N, Lorig K. (2013). Successes of a national study of the chronic disease self-management program: Meeting the triple aim of health care reform. Med Care, 51(11), 992-998.

2. Ritchie L, Wright-St Clair VA, Keogh J, Gray M. (2014). Community integration after traumatic brain injury: A systematic review of the clinical implications of measurement and service provision for older adults. Arch Phys Med Rehabil, 95(1), 163-174.

3. No authors listed. Study protocol for the world health organization project to develop a quality of life assessment instrument (WHOQOL). (1993). Qual Life Res, 2(2),153-159.

4. Trompenaars FJ, Masthoff ED, Van Heck GL, De Vries J, Hodiamont PP. (2007). Relationships between social functioning and quality of life in a population of Dutch adult psychiatric outpatients. Int J Soc Psychiatry, 53(1), 36-47.

5. van Delft-Schreurs CC, van Bergen JJ, de Jongh MA, van de Sande P, Verhofstad MH, deVries J. (2014). Quality of life in severely injured patients depends on psychosocial factors rather than on severity or type of injury. Injury, 45(1), 320-326.

6. Dajpratham P, Tantiniramai S, Lukkanapichonchut P. (2011). Health related quality of life among the thai people with unilateral lower limb amputation. J Med Assoc Thai, 94(2), 250-255.

7. Masthoff ED, Trompenaars FJ, Van Heck GL, Hodiamont PP, De Vries J. (2006). Quality of life and psychopathology: Investigations into their relationship. Aust N Z J Psychiatry, 40(4), 333-340.
8. Arnold R, Ranchor AV, Koeter GH, de Jongste MJ, Wempe JB, ten Hacken NH, Otten V, Sanderman R. (2006). Changes in personal control as a predictor of quality of life after pulmonary rehabilitation. Patient Educ Couns, 61(1), 99-108.
9. Coffey L, Gallagher P, Desmond D. (2014). Goal pursuit and goal adjustment as predictors of disability and quality of life among individuals with a lower limb amputation: a prospective study.Arch Phys Med Rehabil, 95(2), 244-252.
10. Skevington SM, Lotfy M, O'Connell KA, WHOQOL Group. (2004). The World Health Organization's WHOQOL-BREF quality of life assessment: Psychometric properties and results of the international field trial. A report from the WHOQOL group. Qual Life Res, 13(2), 299-310.
11. Lai BPY, Tang CS, Chung TKH. (2009). Age-specific correlates of quality of life in Chinese women with cervical cancer. Supportive Care in Cancer, 17(3), 271-278.
12. Falsarella GR, Coimbra IB, Neri AL, Barcelos CC, Lavras Costallat LT, Fernandes Carvalho OM, Valente Coimbra AM. (2012). Impact of rheumatic diseases and chronic joint symptoms on quality of life in the elderly. Arch Gerontol Geriatr, 54(2), E77-82.
13. Graham CD, Rose MR, Grunfeld EA, Kyle SD, Weinman J. (2011). A systematic review of quality of life in adults with muscle disease. J Neurol, 258(9), 1581-1592.
14. de Franca IS, Coura AS, de Franca EG, Basilio NN, Souto RQ. (2011). Quality of life of adults with spinal cord injury: A study using the WHOQOL-bref. Rev Esc Enferm USP, 45(6), 1364-1371.
15. Engel GL. (1977). The need for a new medical model: a challenge for biomedicine. Science,8; 196(4286):129-136.
16. Yeung P, Towers A. (2014). An exploratory study examining the relationships between the personal, environmental and activity participation variables and quality of life among young adults with disabilities. Disabil Rehabil, 36(1), 63-73.
17. Ackerley SJ, Gordon HJ, Elston AF, Crawford LM, McPherson KM. (2009). Assessment of quality of life and participation within an outpatient rehabilitation setting. Disabil Rehabil, 31(11), 906-913.
18. De Vries J, Den Oudsten BL. (2015) Handleiding WHOQOL-100 en WHOQOL-BREF. Herziene versie [manual WHOQOL-100 and WHOQOL-BREF. Revised version] Department of Medical and Clinical Psychology, Tilburg University.
19. Canavarro MC, Pereira M. (2012). Factor structure and psychometric properties of the european portuguese version of a questionnaire to assess quality of life in HIV-infected adults: The WHOQOL-HIV-bref. AIDS Care, 24(6), 799-807.
20. Masthoff ED, Trompenaars FJ, Van Heck GL, Hodiamont PP, De Vries J. (2005).Validation of the WHO quality of life assessment instrument (WHOQOL-100) in a population of Dutch adult psychiatric outpatients. Eur Psychiatr, 20(7), 565-573.
21. Resource document. Centraal Bureau voor de Statistiek. http://www.cbs.nl/nl-NL/menu/methoden/classificaties/overzicht/isced/default.htm. (2015).
22. Altman DG.(1991). Practical statistics for medical research. First ed. London: Chapman & Hall.

23. Resource document. Revalidatie Nederland.
http://jaarbeeldrevalidatie.nl/jaarbeeld12/. (2014)
24. Ignacio Cuesta-Vargas A, Gonzalez-Sanchez M, Jesus Casuso-Holgado M. (2013). Effect on health-related quality of life of a multimodal physiotherapy program in patients with chronic musculoskeletal disorders. Health Qual Life Outcomes, 16, 11-19.
25. Wong WS, Lam HMJ, Chow YF, Chen PP, Lim HS, Wong S, Fielding R. (2014). The effects of anxiety sensitivity, pain hypervigilance, and pain catastrophizing on quality of life outcomes of patients with chronic pain: a preliminary, cross-sectional analysis. Qual Life Res, 23(8), 2333-2341.
26. Skevington SM, McCrate FM. (2012). Expecting a good quality of life in health: Assessing people with diverse diseases and conditions using the WHOQOL-BREF. Health Expectations, 15(1), 49-62.

Chapter 3

Subjective cognitive dysfunction in rehabilitation outpatients with musculoskeletal disorders or chronic pain

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Eur J Phys Rehabil Med. 2017 Aug;53(4):582-589

Abstract

Background: rehabilitation patients, without brain damage, sometimes complain about poor concentration and problems with their memory. The magnitude and associations, of this cognitive dysfunction, with different factors is unclear.
*Aim***:** To determine the magnitude of cognitive dysfunction in rehabilitation outpatient and to explore its associations with patient characteristics, diagnosis, surgery, pain, stress, anxiety and depression.
Design: Cross sectional.
Setting: Rehabilitation outpatients.
Population: Between July 2009 and January 2012, 274 rehabilitation outpatients were included and divided in 8 different groups through diagnosis.
Methods: Cognitive functioning was assessed using the cognitive failure questionnaire and compared with the general Dutch population. Associations of gender, age, diagnosis, recent surgery, pain and stress coping ability with cognitive function was explored. Mediation of depression and anxiety was explored.
Results: The rehabilitation patients had a significantly higher score on the CFQ (mean (SD) = 35.9 (13.4)) when compared to the general Dutch population (mean (SD) = 31.8 (11.1)). Mean difference is 4.1, 95% 2confidence interval 2.60 to 5.60 In the stepwise linear regression analysis only gender, diagnosis and stress coping ability were significantly associated. A significant mediation effect was found of anxiety (p=<0.001) and depression (p=<0.005) between stress coping ability and cognitive function.
Conclusions: Rehabilitation outpatients experience more cognitive problems in comparison to the general Dutch population. Reported dysfunction of cognition in rehabilitation outpatients are associated with stress coping ability and for a small amount to gender and diagnosis. The association of stress coping ability and cognitive dysfunction is mediated by depression and anxiety. Women tend to report more dysfunctional cognition compared to men. Patient characteristics, surgery and experienced pain have no significant influence on the experienced cognitive dysfunction**.**
Clinical rehabilitation impact: Cognitive problems reported by patients should be addressed by adapting the rehabilitation program, for instance write down instructions, repeat explanations and take more time for instructions. . Cognitive problems in rehabilitation patients without brain damage is probably a stress coping problem and can be addressed by boosting resilience. Targeting depression or anxiety is another option of treatment cognition if those are mediating between stress coping and cognitive problems.

Introduction

In rehabilitation inpatients, without brain injury, cognitive dysfunction does occur.[1, 2] Cognitive dysfunction has been found to be associated with different factors including gender, age, diagnosis, surgery, pain, stress, anxiety and depression.[3-13]

There are many hypotheses regarding the associations between cognitive dysfunction and the factors mentioned above. Some hypotheses are biomedical and describe that anoxia, hypoperfusion or micro-emboli may occur during surgery causing brain damage, resulting in cognitive dysfunction.[1, 14] Other hypotheses are biopsychosocial, and describe more complicated pathways to the cognitive dysfunction.[15-18] In patients suffering from medical unexplained symptoms such as irritable bowel syndrome, chronic pain, fatigue and stress, a complicated interaction between different systems and structures has been described to maintain homeostasis including the hypothalamic-pituitary-adrenal axis, the autonomic nervous system, the immune system and the prefrontal cortex.[3, 19-23] These systems interact with endogenous and exogenous stimuli in a protective and beneficial way but can become deleterious and may cause, among other things, cognitive dysfunction. Rehabilitation outpatients are exposed to stressful circumstances and stress factors like surgery and pain.[24, 25]
Stress, chronic and acute, causes an imbalance of the neural circuitry subserving cognition, anxiety and mood.[26] Therefore according to the hypotheses above it is no surprise that patients may complain, along with a change in mood and anxiety, about cognitive dysfunction. Little is known about the extent of this problem nor is it clear if patient characteristics, diagnosis, surgery, pain, are associated with the cognitive dysfunction and if there is a mediating role of depression and anxiety in rehabilitation outpatients.
When there is no clear cue for cognitive dysfunction like brain damage or old age, it may stay unnoticed during the rehabilitation. Cognitive dysfunction such as poor functioning of memory, concentration or problem solving, has a negative influence on the outcome of rehabilitation programs.[27-29] When cognitive dysfunction is recognized, the rehabilitation program need to be adapted,[30] for instance write down instructions, repeat explanations and take more time for instructions.
The aim of the study is to determine the magnitude of cognitive dysfunction in rehabilitation outpatient and to explore its associations with patient characteristics, diagnosis, surgery, pain, anxiety, stress and depression.

Materials and methods

This study is assessed by the Medical ethics Review Board and they state that it fulfils all the requirements of our University Hospital for publication of patient data on 08-20-2015 (2015/348). All patients signed an informed consent.
Participants
Between July 2009 and January 2012, 327 outpatients (≥18 years) from the Department of Rehabilitation Medicine of the University Medical Centre Groningen were referred to a psychologist with experience in patients undergoing rehabilitation. They were referred by a rehabilitation physician for a psychological assessment and/or treatment. All the referred out clinic patients were included. Medical referral diagnosis were used to form 8 different diagnosis groups. Excluded from this consecutive study sample were patients with possible brain damage or organ failure. Before the first meeting with the psychologist, a set of questionnaires was sent by mail with the request to fill out the questionnaires and bring these to the first

session. An informed consent was sent together with the questionnaires. The following patient characteristics were collected during the intake procedure; gender, education (according to the International Standard Classification of Education)[31], marital status and age. Also the highest and lowest pain intensity, experienced in the last week, assessed on a numeric rating scale from 0 to 10 was collected. From the medical records data regarding recent surgery (< 3 months ago) and the referral diagnosis of the rehabilitation physician was collected.

Questionnaires

This study used questionnaires to assess cognitive functioning, the stress coping ability, depression and anxiety. Self-reported cognitive functioning was assessed using the cognitive failure questionnaire (CFQ).[32, 33] The CFQ is a 25-item self-report questionnaire assessing failures in perception, memory, and motor function in the completion of everyday tasks in the past 6 months. Individuals were asked to rate the frequency of experiences and behaviors on a 5-point scale from 0 (never), to 4 (very often). In this study, the sum score (range 1-100) was used. Higher scores indicate more cognitive failures. The CFQ is shown to have excellent psychometric properties, CFQ reliability (r) over 24 months is 0.71, the inter-item reliability Cronbach's α of the CFQ is 0.92.[34]

The Connor-Davidson Resilience Scale (CD-RISC) was used to estimate the stress coping ability of a patient.[35] The CD-RISC is a 25 item questionnaire. Each item is rated on a 5-pont scale, higher scores reflecting greater resilience. Resilience may be viewed as a measure of stress coping ability.[35] There is no gold standard for resilience yet but in a review of different resilience questionnaires the CD-RISC was 1 of the 3 questionnaires with the best psychometric properties.[36]

The hospital anxiety and depression scale (HADS) was used to assess anxiety and depression.[37] This scale is divided into an anxiety subscale (HADS-A) and a depression subscale (HADS-D), both containing 7 intermingled items. During the development of this scale the 'noise' from somatic disorders on the scores, all symptoms of anxiety or depression also relating to physical disorder, such as dizziness, headaches, insomnia, anergia and fatigue, were excluded.[34] In patients with musculoskeletal disorders the depression subscale is stable. The reported Chronbach alpha was .83 for the anxiety subscale and .84 for the depression subscale, indicating adequate internal consistency.[38]

Statistical procedures

Data was anonymized and analyzed using IBM SPSS Statistics (v.20). P-P and Q-Q plots were used to assess normal distribution of dependent variables. Results are significant at $p \leq 0.05$ unless stated otherwise. To analyze differences in means of the CFQ in rehabilitation outpatients with a general Dutch population the confidence interval (CI) for difference in means was calculated.[30]

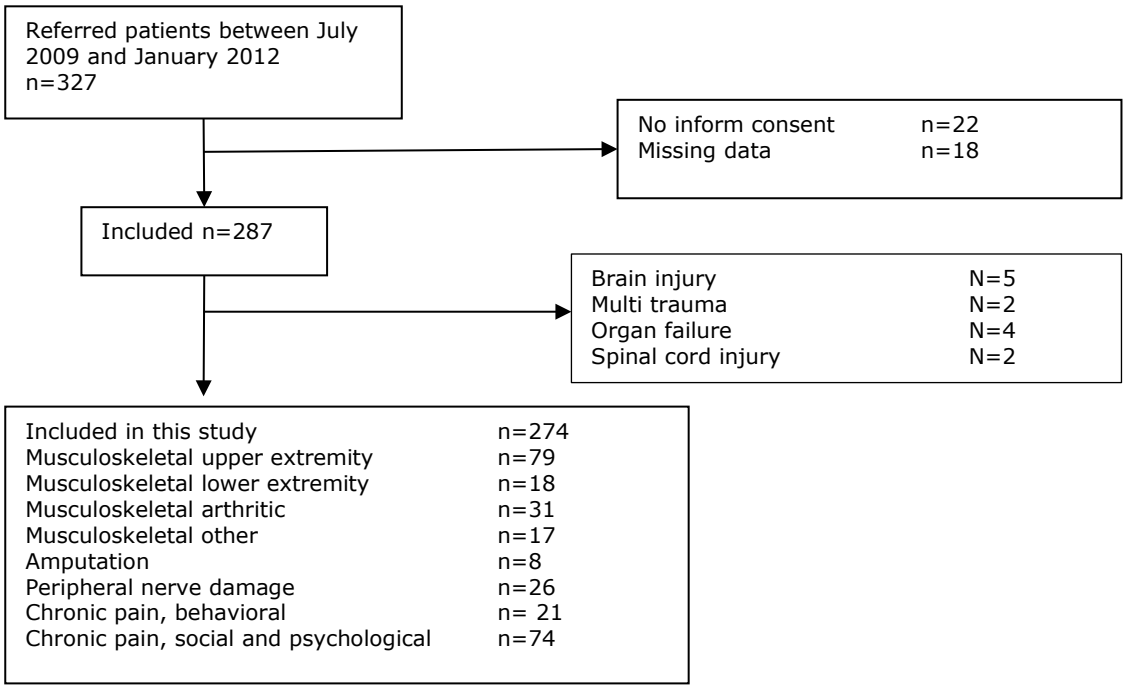
A Pearson Chi-Square test and ANOVA were used to analyze if gender, education, social status, age, HADS-D, HADS-A, pain, CFQ and CD-RISC total score, differed between diagnosis groups. Education was split according to the international Standard Classification of Education (ISCED) 2011; Low education equals the ISCED level 0-4, middle the level 5 and high the level 6-9.[31] For (regression) analyses several dummy variables were computed. Social status was dichotomized into living alone (living alone and living with the family or a partner), diagnosis was

dichotomized into musculoskeletal (upper extremity, lower extremity, arthritic and other) and the other 4 groups (chronic pain complex/not complex, peripheral nerve damage and amputation). To analyze the association between gender, age, diagnosis, surgery, pain and stress coping ability, a hierarchical step wise regression analysis was used with the sum score CFQ as dependent variable. In the first step we entered gender and age, in the second the diagnosis, in the third surgery and pain intensity, in the fourth stress coping ability. Interaction effects were explored and residuals were checked for a normal distribution. Anxiety and depression were added in the fifth step to check mediation. Anxiety and depression were used in a mediation model using stress coping ability as independent variable, cognition as dependent variable and depression and anxiety as mediators. PROCESS v2.16 add on for SPSS by Hayes was used for mediation calculation.[39]

Results

Of all the referred patients (n=327) some did not want to participate (n=22) and some questionnaires contained too much missing data (n=18). Of the remaining 287 patients, 13 patients had an organ failure or a (presumably) central neurologic problem and were excluded. The most common referral diagnosis, of the included 274 patients, was musculoskeletal disorder (53%), followed by chronic pain (35%). The musculoskeletal group was divided in 4 subgroups, 3 depending on the location of their musculoskeletal disorder, upper extremity, lower extremity and other such as spine or trunk, and 1 arthritic disorder group including rheumatoid arthritis. The pain group was divided in 2 subgroups. Social and psychological factors played a substantial role in maintaining the pain in the first chronic pain group (complex) and behavior such as overuse played a substantial role in maintaining the pain in the second chronic pain group (not complex).

Figure 1 Flowchart of inclusion procedure.



The group of peripheral nerve damage (9%) and a small group of patients with an amputation (3%) are the last 2 of the total of 8 groups (Figure 1).
No significant differences were found between the 8 different diagnosis groups with regard to gender, education, social status, age and stress coping ability (Table 1).

Table 1 Characteristics of participants of the total group, the musculoskeletal group, the chronic pain group and subgroups.

	Total group **n=274**	**Musculoskeletal** **n= 145**				**Chronic pain** **n= 95**		**Peripheral nerve damage** **n=26**	**Amputation** **n=8**	**P value ***
		Upper extremity n=79	Lower extremity n=18	Other n=17	Arthritic n=31	Complex n=74	Not Complex n=21			
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Gender	200 (73.0)	59 (74.7)	15(83.3)	13(76.5)	23(74.2)	49(66.2)	16(76.2)	22(84.6)	3(37.5)	0.192†
Education										0.288†
--Low/lowest	86 (31.3)	22 (27.9)	4(22.2)	4 (22.2)	13(41.9)	28 (37.8)	6 (28.6)	7(26.9)	2(25.0)	
--Medium	121 (44.2)	40 (50.6)	5(27.8)	7(41.2)	11 (35.5)	34 (45.9)	7 (33.3)	13(50.0)	4(50)	
--High	67 (24.5)	17 (21.5)	9(50.0)	6 (35.3)	7 (22.6)	12 (16.2)	8 (38.1)	6(23.1)	2(25)	
Social status										0.234†
--Living alone	61 (22.3)	13 (16.5)	4(22.2)	7 (41.4)	7 (22.6)	17 (23.0)	8 (38.1)	4(15.4)	1(12.5)	
--With person(s)	231 (77.7)	66(83.5)	14(77.8)	10(58.6)	24(77.4)	57 (77)	13(61.9)	22(84.6)	7(87.5)	
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Age, mean (sd)	40.6 (14.6)	38.9(14.6)	30.4(15.2)	44.8(14.0)	44.5 (15.2)	41.2(13.0)	40.3(16.9)	41.7(13.2)	36.6(13.9)	0.122‡
HADS-D§	6.9 (4.4)	6.0(4.5)	6.1(4.0)	7.9(4.9)	6.2(4.1)	8.7(4.3)	6.5(3.6)	6.0(4.5)	4.8(4.5)	0.003‡
HADS-A||	8.3 (4.8)	7.3 (4.8)	7.9(3.9)	10.5(5.1)	7.6(4.8)	10.5(4.9)	7.5(3.9)	6.8(4.0)	5.7(4.1)	<0.010‡
Pain-high	5.2(3.5)	5.5(3.2)	5.7(3.3)	2.7(3.5)	4.7(3.7)	6.0(3.2)	5.2(3.6)	4.5(4.3)	2.9(4.2)	0.009‡
Pain-low	3.0(2.7)	3.0(2.5)	3.0(3.0)	1.7(2.4)	3.0(2.9)	3.4(2.4)	2.6(2.9)	2.9(3.2)	1.3(2.6)	0.198‡
CFQ total score	35.9(13.3)	33.7(11.5)	32.8(14.0)	40.3(12.8)	33.4(12.3)	41.2(13.6)	35.9(14.7)	32.5(14.7)	29.3(11.3)	0.003‡
CD-RISC	63.2(14.1)	62.5(14.7)	65.3(15.0)	61.0 (15.9)	65.9(14.1)	60.0(13.3)	62.9(11.5)	67.5(14.0)	73.4(11.6)	0.840‡

Posthoc analysis of the HADS-D showed significant difference between upper extremity and complex chronic pain; Posthoc analysis of the HADS-A showed significant difference between upper extremity and complex chronic pain and between complex chronic pain and peripheral nerve damage; Posthoc analysis of the pain high showed significant difference between upper extremity and other; Posthoc analysis of the CFQ total showed significant difference between complex chronic pain and upper extremity.*Significance differences between groups †: chi square test, ‡: ANOVA CFQ=cognitive failure questionnaire, HADS = hospital anxiety and depression scale §) depression subscale, ||) anxiety subscale

The rehabilitation patients had a significantly higher score on the CFQ (mean (SD) = 35.9 (13.4)) when compared to the general Dutch population (mean (SD) = 31.8 (11.1)). Mean difference 4.1, 95% confidence interval 2.6 to 5.6.
In the stepwise linear regression analysis only gender, diagnosis and stress coping ability were significantly associated, after stress coping ability (CD-RISC) was entered in the fourth step. There were no significant interaction effects (Table 2). The explained variance of the model was 0.159. Residuals were normally distributed.

Table 2 Results of the stepwise regression analyses of the CFQ as dependent variables. With 4 steps of independent variables.

	B	**SE B**	**Sig**	**95%Confidence interval**		**R Square Change**
				Lower bound	**Upper bound**	
Step 1						0.017
Gender/male	-3.532	1.713	.040	-6.905	-.159	
Age	.039	.053	.465	-.066	.144	
Step 2						0.019*
Diagnosis†	-3.304	1.512	.030	-6.281	-.328	
Step 3						0.018
Surgery‡	-3.567	2.253	.115	-8.003	.868	
Pain high§	.110	.339	.747	-.558	.777	
Pain low||	-.342	.444	.442	-1.215	.532	
Step 4						0.106**
CD-RISC	-.311	.054	<.001	-.417	-.205	
Constant	57.632	4.647	<.001	48.482	66.781	

* sig < 0.05. ** <0.001 * . †. Musculosketetal yes, no. ‡. Surgery <3 month before intake, yes, no. §. Highest experienced pain level last week on the numeric rating scale ||. Lowest experienced pain level last week on the numeric rating scale. B = unstandardized coefficients. For gender the reference group was female. for surgery the reference group was no surgery. For was musculoskeletal disorders the reference groups was chronic pain, peripheral nerve damage and amputation combined.

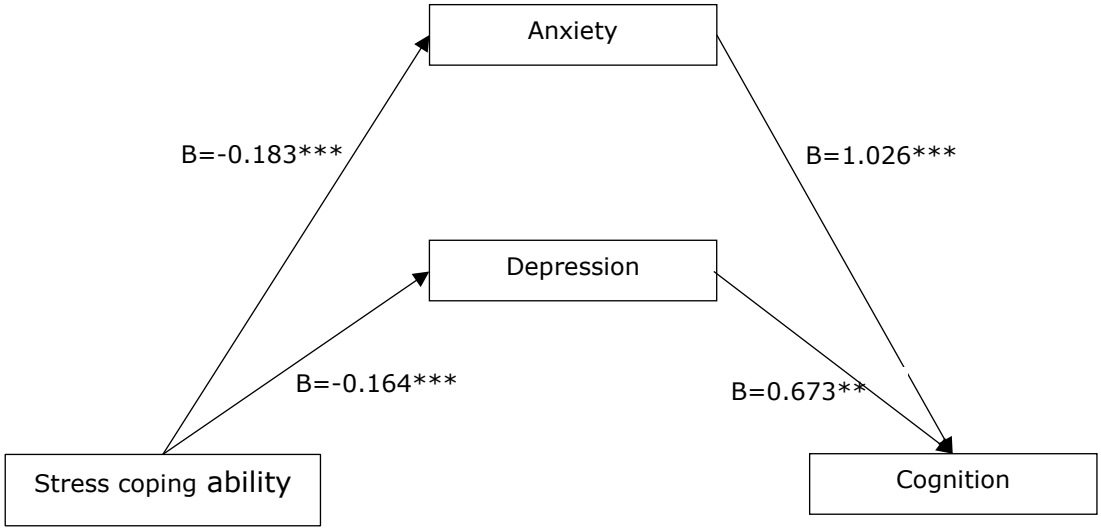
Table 3 Results of the stepwise regression analyses of the CFQ as dependent variables. With 5 steps of independent variables.

	B	**SE B**	**Sig**	**95%Confidence interval**		**R Square Change**
				Lower bound	**Upper bound**	
Step 1						0.017
Gender/male	-3.232	1.498	.032	-6.181	-.282	
Age	-.014	.048	.765	-.108	.080	
Step 2						0.019*
Diagnosis†	-1.554	1.335	.245	-4.182	1.074	
Step 3						0.018
Surgery‡	-2.528	1.977	.202	-6.421	1.365	
Pain high§	.092	.298	.758	-.494	.678	
Pain low||	-.670	.389	.086	-1.437	.096	
Step 4						0.106**
CD-RICS	-.024	.056	.669	-.135	.087	
Step 5						0.204**
HADS-A	.973	.219	<.001	.542	1.404	
HADS-D	.746	.240	.002	.273	1.219	
Constant	34.946	2.421	<.001	30.180	39.712	

* sig =< 0.05. ** sig=<0.001 †. Musculosketetal yes. no. ‡. Surgery <3 month before intake. yes. no. §. Highest experienced pain level last week on the numeric rating scale ||. Lowest experienced pain level last week on the numeric rating scale. B = unstandardized coefficients SE = standard error. For gender the reference group was female. for surgery the reference group was no surgery. For was musculoskeletal disorders the reference groups was chronic pain, peripheral nerve damage and amputation combined.

In a fifth step Anxiety (HADS-A) and depression (HADS-D) were entered. Association between stress coping ability and CFQ was reduced and no longer significant, indicating a strong mediating effect of the HADS-A and HADS-D.
A significant mediation effect was found of anxiety (p=<0.001) and depression (p=0.006) between stress coping ability and cognitive function (Figure 2). Gender and diagnosis did not have any mediation effect.

Figure 2
Mediation model.



Mediation model showing that stress coping ability, (independent variables) on cognition (dependent) is mediated by anxiety and depression. Total effect model B = -0.324, t(272)=-6.037, *p*=<.001 ** p=<0.005 *** p=<0.001

Discussion

Rehabilitation outpatients experience more cognitive problems compared to the general Dutch population. This difference confirms the observation that a proportion of the rehabilitation outpatients complained about cognitive functioning. Of the patient characteristics analyzed in this study gender appeared to be significantly related to the CFQ scores but the effect was small (1.7% explained variance). Diagnosis also had a small effect (1.9% explained variance). Stress coping ability (CD-RISC) had the foremost influence on the model (11% explained variance). Beside the direct effect there was a substantial mediating effect of anxiety and depression on cognition (Table 3). Entering anxiety and depression in the fifth step reduced the association between stress coping ability and cognitive problems. That is a sign of mediation (Figure 2). The presented model is simple and the discussion about a (more complicated) model is going on.[19-21, 40] This model provides the clinician with more possibilities to modify the rehabilitation program. The obvious

solution is to adapt the program as described in the introduction. Other opportunities are strengthening the stress coping ability or treatment of anxiety and depression.[41, 42]

Although the difference with the general Dutch population was clinically small, it is relevant in rehabilitation because cognition is one important determinant of rehabilitation outcome.[27, 28]

The expected association with, surgery or pain was not found. Other studies did find a significant association between surgery and pain and cognition.[1, 2, 6, 7] One explanation of this difference in outcomes is that in previous studies, stress coping ability, depression and anxiety was not included into the analyses.[43] Another explanation for this difference is that in our study, patients were included up to 3 months after surgery. Cognitive decline was found to be most distinct in the first 2 weeks after surgery.[14]

In a study including patients with chronic pain, an association was found between pain and cognitive dysfunction but depression made the strongest unique contribution to the cognitive dysfunction.[3] A study in fibromyalgia patients found that pain played an important role in cognitive dysfunction.[44] Sleep disturbance and depression were referred to as factors influencing cognition.[45] All mentioned studies acknowledge the role of depression in disrupting cognition.[1-3, 6, 7, 14, 15, 44, 45] In our study depression, anxiety mediated cognitive problems. Although the pathway is not yet revealed, our study suggests that perceived cognitive dysfunction may be an indicator of an imbalance of the neural circuitry resulting in cognitive problems, anxiety or depressive symptoms. This imbalance is caused by acute and chronic stress as experienced by rehabilitation patients.[24]

It is safe to assume that the patients in this study experienced stress.[24, 46] This is stress for example about their health, the pain they experience, and frustration about the things they can't do, like work or hobby, due to their disorder. Stress is linked to dysfunctional cognitions, major depression and anxiety in several studies.[19, 47]

The strength of this study is that it included different diagnoses within the rehabilitation outpatients, included different possible causes of the cognitive problem and the mediating factors.

Study limitations

The weakness of this study is the use of one screening instrument for cognitive dysfunction. The CFQ is a subjective measure of cognitive functioning. A study about cognitive functioning in bipolar disorders showed no association between cognitive complaints and objective cognitive functioning, but cognitive complaints were strongly related to depressive symptoms.[48] Other studies found a relationship between objective testing and subjective questionnaire as the CFQ and even that perceived cognitive problems predict cognitive decline at an earlier stage than objective tests.[49] Whereas another study concluded white matter lesions were associated with subjective cognitive failures, even in the absence of objective cognitive impairment.[50]

Conclusions
Rehabilitation outpatients experience more cognitive problems in comparison to the general Dutch population. Reported dysfunction of cognition in rehabilitation outpatients are associated with stress coping ability and for a small amount to gender and diagnosis. The association of stress coping ability and cognitive dysfunction is mediated by depression and anxiety. Women tend to report more dysfunctional cognition compared to men.

Declaration of interest
The authors declare no conflicts of interests.
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Acknowledgements
The authors wish to thank V. Leseman, MSc, psychologist for helping with the start of the study.

References

1. Purohit M, Goldstein R, Nadler D, Mathews K, Slocum C, Gerrard P, et al. Cognition in patients with burn injury in the inpatient rehabilitation population. Arch Phys Med Rehabil 2014; 95: 1342-9.
2. Woods AJ, Mark VW, Pitts AC and Mennemeier M. Pervasive cognitive impairment in acute rehabilitation inpatients without brain injury. PM R 2011; 3: 426-32.
3. Roth RS, Geisser ME, Theisen-Goodvich M and Dixon PJ. Cognitive complaints are associated with depression, fatigue, female sex, and pain catastrophizing in patients with chronic pain. Arch Phys Med Rehabil 2005; 86: 1147-54.
4. Keizer AM, Hijman R, van Dijk D, Kalkman CJ and Kahn RS. Cognitive self-assessment one year after on-pump and off-pump coronary artery bypass grafting. Ann Thorac Surg 2003; 75: 835-8; discussion 838-9.
5. Pechtel P and Pizzagalli DA. Effects of early life stress on cognitive and affective function: an integrated review of human literature. Psychopharmacology (Berl) 2011; 214: 55-70.
6. Berryman C, Stanton TR, Jane Bowering K, Tabor A, McFarlane A and Lorimer Moseley G. Evidence for working memory deficits in chronic pain: a systematic review and meta-analysis. Pain 2013; 154: 1181-96.
7. Rudolph JL, Schreiber KA, Culley DJ, McGlinchey RE, Crosby G, Levitsky S, et al. Measurement of post-operative cognitive dysfunction after cardiac surgery: a systematic review. Acta Anaesthesiol Scand 2010; 54: 663-77.
8. Vardy J, Rourke S and Tannock IF. Evaluation of cognitive function associated with chemotherapy: a review of published studies and recommendations for future research. J Clin Oncol 2007; 25: 2455-63.
9. Wu CL, Hsu W, Richman JM and Raja SN. Postoperative cognitive function as an outcome of regional anesthesia and analgesia. Reg Anesth Pain Med 2004; 29: 257-68.

10. Schwabe L, Joels M, Roozendaal B, Wolf OT and Oitzl MS. Stress effects on memory: An update and integration. Neurosci Biobehav Rev 2012; 36: 1740-9.
11. Paleacu D, Shutzman A, Giladi N, Herman T, Simon ES and Hausdorff JM. Effects of pharmacological therapy on gait and cognitive function in depressed patients. Clin Neuropharmacol 2007; 30: 63-71.
12. Wessels AM, Pouwer F, Geelhoed-Duijvestijn PH, Snel M, Kostense PJ, Scheltens P, et al. No evidence for increased self-reported cognitive failure in Type 1 and Type 2 diabetes: a cross-sectional study. Diabet Med 2007; 24: 735-40.
13. Lucassen PJ, Pruessner J, Sousa N, Almeida OFX, Van Dam AM, Rajkowska G, et al. Neuropathology of stress. Acta Neuropathol 2014; 127: 109-35.
14. Cormack F, Shipolini A, Awad WI, Richardson C, McCormack DJ, Colleoni L, et al. A meta-analysis of cognitive outcome following coronary artery bypass graft surgery. Neurosci Biobehav Rev 2012; 36: 2118-29.
15. van Hoogmoed D, Fransen J, Bleijenberg G and van Riel P. Physical and psychosocial correlates of severe fatigue in rheumatoid arthritis. Rheumatology (Oxford) 2010; 49: 1294-302.
16. Hutchison M, Comper P, Mainwaring L and Richards D. The influence of musculoskeletal injury on cognition: implications for concussion research. Am J Sports Med 2011; 39: 2331-7.
17. Burnes DP and Burnette D. Broadening the etiological discourse on Alzheimer's disease to include trauma and posttraumatic stress disorder as psychosocial risk factors. J Aging Stud 2013; 27: 218-24.
18. Whittaker R, Kemp S and House A. Illness perceptions and outcome in mild head injury: a longitudinal study. J Neurol Neurosurg Psychiatry 2007; 78: 644-6.
19. Kennedy PJ, Clarke G, Quigley EMM, Groeger JA, Dinan TG and Cryan JF. Gut memories: Towards a cognitive neurobiology of irritable bowel syndrome. Neurosci Biobehav Rev 2012; 36: 310-40.
20. Hennig-Fast K, Werner NS, Lermer R, Latscha K, Meister F, Reiser M, et al. After facing traumatic stress: brain activation, cognition and stress coping in policemen. J Psychiatr Res 2009; 43: 1146-55.
21. Sandstrom A, Peterson J, Sandstrom E, Lundberg M, Nystrom IL, Nyberg L, et al. Cognitive deficits in relation to personality type and hypothalamic-pituitary-adrenal (HPA) axis dysfunction in women with stress-related exhaustion. Scand J Psychol 2011; 52: 71-82.
22. Bol Y, Duits AA, Lousberg R, Hupperts RM, Lacroix MH, Verhey FR, et al. Fatigue and physical disability in patients with multiple sclerosis: a structural equation modeling approach. J Behav Med 2010; 33: 355-63.
23. Sarzi-Puttini P, Atzeni F and Mease PJ. Chronic widespread pain: from peripheral to central evolution. Best Pract Res Clin Rheumatol 2011; 25: 133-9.
24. Vincent HK, Horodyski M, Vincent KR, Brisbane ST and Sadasivan KK. Psychological Distress After Orthopedic Trauma: Prevalence in Patients and Implications for Rehabilitation. PM R 2015; 7: 978-89.
25. Putukian M. The psychological response to injury in student athletes: a narrative review with a focus on mental health. Br J Sports Med 2016; 50: 145-8.

26. McEwen BS, Eiland L, Hunter RG and Miller MM. Stress and anxiety: structural plasticity and epigenetic regulation as a consequence of stress. Neuropharmacology 2012; 62: 3-12.
27. Seematter-Bagnoud L, Lecureux E, Rochat S, Monod S, Lenoble-Hoskovec C and Bula CJ. Predictors of functional recovery in patients admitted to geriatric postacute rehabilitation. Arch Phys Med Rehabil 2013; 94: 2373-80.
28. O'Neill BF and Evans JJ. Memory and executive function predict mobility rehabilitation outcome after lower-limb amputation. Disabil Rehabil 2009; 31: 1083-91.
29. Bellelli G, Frisoni GB, Pagani M, Magnifico F and Trabucchi M. Does cognitive performance affect physical therapy regimen after hip fracture surgery?. Aging Clin Exp Res 2007; 19: 119-24.
30. Coutu MF, Durand MJ, Marchand A, Labrecque ME, Berbiche D and Cadieux G. Factors associated with generalized anxiety in workers undergoing work rehabilitation for persistent musculoskeletal pain. Disabil Rehabil 2013; 35: 1599-607.
31. Anonymous ISCED (2019, accessed https://www.cbs.nl/nl-nl/onze-diensten/methoden/classificaties/onderwijs-en-beroepen/isced/isced-f-2013-richting.
32. Broadbent DE, Cooper PF, FitzGerald P and Parkes KR. The Cognitive Failures Questionnaire (CFQ) and its correlates. Br J Clin Psychol 1982; 21 (Pt 1): 1-16.
33. Wallace JC, Kass SJ and Stanny CJ. The cognitive failures questionnaire revisited: dimensions and correlates. J Gen Psychol 2002; 129: 238-56.
34. Bridger RS, Johnsen SA and Brasher K. Psychometric properties of the Cognitive Failures Questionnaire. Ergonomics 2013; 56: 1515-24.
35. Connor KM and Davidson JR. Development of a new resilience scale: the Connor-Davidson Resilience Scale (CD-RISC). Depress Anxiety 2003; 18: 76-82.
36. Windle G, Bennett KM and Noyes J. A methodological review of resilience measurement scales. Health Qual Life Outcomes 2011; 9: 8,7525-9-8.
37. Zigmond AS and Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983; 67: 361-70.
38. Pallant JF and Bailey CM. Assessment of the structure of the Hospital Anxiety and Depression Scale in musculoskeletal patients. Health Qual Life Outcomes 2005; 3: 82.
39. Hayes AF. part 2 mediation analysis. In: Anonymous *Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression-Based Approach*, 2013, p.83.
40. Rutten BPF, Hammels C, Geschwind N, Menne-Lothmann C, Pishva E, Schruers K, et al. Resilience in mental health: linking psychological and neurobiological perspectives. Acta Psychiatr Scand 2013; 128: 3-20.
41. Leppin AL, Gionfriddo MR, Sood A, Montori VM, Erwin PJ, Zeballos-Palacios C, et al. The efficacy of resilience training programs: a systematic review protocol. Syst Rev 2014; 3: 20,4053-3-20.
42. Apostolo J, Bobrowicz-Campos E, Rodrigues M, Castro I and Cardoso D. The effectiveness of non-pharmacological interventions in older adults with depressive disorders: A systematic review. Int J Nurs Stud 2016; 58: 59-70.

43. Dick BD and Pillai Riddell R. Cognitive and school functioning in children and adolescents with chronic pain: a critical review. Pain Res Manag 2010; 15: 238-44.
44. Dick BD, Verrier MJ, Harker KT and Rashiq S. Disruption of cognitive function in fibromyalgia syndrome. Pain 2008; 139: 610-6.
45. Naismith SL, Rogers NL, Lewis SJ, Terpening Z, Ip T, Diamond K, et al. Sleep disturbance relates to neuropsychological functioning in late-life depression. J Affect Disord 2011; 132: 139-45.
46. Haverkamp GL, Torensma B, Vergouwen AC and Honig A. Psychological Distress in the Hospital Setting: A Comparison between Native Dutch and Immigrant Patients. PLoS One 2015; 10: e0130961.
47. Beck AT. The evolution of the cognitive model of depression and its neurobiological correlates. Am J Psychiatry.2008 Aug;165(8):969-77.
48. van der Werf-Eldering MJ, Schouws S, Arts B and Jabben N. Cognitive dysfunction in bipolar disorder: determinants and functional outcome. Tijdschr Psychiatr 2012; 54: 709-18.
49. Dufouil C, Fuhrer R and Alperovitch A. Subjective cognitive complaints and cognitive decline: consequence or predictor? The epidemiology of vascular aging study. J Am Geriatr Soc 2005; 53: 616-21.
50. de Groot JC, de Leeuw FE, Oudkerk M, Hofman A, Jolles J and Breteler MM. Cerebral white matter lesions and subjective cognitive dysfunction: the Rotterdam Scan Study. Neurology 2001; 56: 1539-45.

Chapter 4

Prosthesis satisfaction in lower limb amputees: a systematic review of associated factors and questionnaires

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Medicine (Baltimore). 2018 Sep;97(39):e12296

Abstract

Objective: The aims of this systematic review were to review the literature regarding factors of influence on patient satisfaction with a transtibial prosthesis, to report satisfaction scores, to present an overview of questionnaires used to assess satisfaction, and examine how these questionnaires operationalize satisfaction. *Methods*: A literature search was performed in PubMed, Embase, PsycInfo, CINAHL, Cochrane, and Web of Knowledge databases up to February 2018 to identify relevant studies. *Results*: Twelve out of 1832 studies met the inclusion criteria. Sample sizes ranged from 14 to 581 participants, mean age ranged from 18 to 70 years, and time since amputation ranged from 3 to 39 years. Seven questionnaires assessed different aspects of satisfaction. Patient satisfaction was influenced by appearance, properties, fit, and use of the prosthesis, as well as aspects of the residual limb. These influencing factors were not relevant for all amputee patients and were related to gender, etiology, liner use, and level of amputation. No single factor was found to significantly influence satisfaction or dissatisfaction. Significant associations were found between satisfaction and gender, etiology, liner use, and level of amputation. *Conclusion*: Relevance of certain factors for satisfaction was related to specific amputee patient groups. Questionnaires assessing satisfaction use different operationalizations, making comparisons between studies difficult.

Acknowledgments: The authors declare that they have no conflict of interest.

Introduction

Regaining mobility is an important rehabilitation objective for patients with a transtibial amputation. Satisfaction with the prosthesis plays a key role in regaining mobility and is important for optimizing use of the prosthesis, preventing rejection, and increasing compliance with the medical regimen.[1,2] Forty percent to 60 % of amputee patients are not satisfied with their prostheses.[3,4] Fifty-seven percent are dissatisfied with the comfort of their prostheses, and over 50% report pain while using their prostheses.[3,4] Rejection of the prosthesis can be seen as the ultimate expression of dissatisfaction with the prosthesis and occurs in up to 31% cases of prostheses prescribed to armed forces service members with lower limb amputations, mainly as a result of technical problems (e.g., "too much fuss" during use and the prosthesis being "too heavy").[5] These findings make (dis)satisfaction with transtibial prostheses a highly relevant issue in lower limb amputee care.[4,5] Patient satisfaction is a key indicator of the quality of care. It plays an important role in the evaluation of outcomes of healthcare services and management of the healthcare budget.[1,2,6-8] Numerous theories and models of patient satisfaction exist, including "the value expectancy model," "the disconfirmation theory," "the attribution theory," and "the need theory." [6,8] Satisfaction is defined in different ways e.g.: "an emotional or affective evaluation of the service based on cognitive processes which were shaped by expectations"; "a congruence of expectations and actual experiences of a health service"; and "an overall evaluation of different

aspects of a health service."[6] In summary, patient satisfaction entails matching patients' experiences with their expectations.
The various questionnaires assessing satisfaction with the prosthesis operationalize satisfaction differently. For example, the Trinity Amputation and Prosthesis Experience Scales (TAPES) assesses satisfaction using a 5- point scale that comprises questions on "color", "noise", "shape", "appearance", "weight", "usefulness", "reliability", "fit", "comfort", and "overall satisfaction." [9,10] The Prosthesis Evaluation Questionnaire (PEQ) uses 2 visual analogue scales to assess overall satisfaction and satisfaction with walking with the prosthesis during the previous 4 weeks.[1]
In this review, prosthesis satisfaction is viewed as a multidimensional and dynamic construct. Prosthesis satisfaction is the patient's subjective and emotional evaluation of (aspects of) the prosthesis that is influenced by the appearance, properties, fit, and use of the prosthesis, as well as aspects of the residual limb. Emotions regarding the prosthesis are also influenced by the patient's psychological state, e.g., depression and anxiety; psychological factors; and person-related characteristics, such as prior experiences, coping, expectations, general values, beliefs, perceptions, and social context.[6,7] Hence, satisfaction with the prosthesis (or prosthesis components) is a biopsychosocial construct that is influenced by all of the aforementioned factors.[1,2,6,7]
Recently, a systematic review analyzed patients' experiences, including satisfaction, with transtibial prosthetic liners.[11] This review has several limitations. First, half of the included studies had small sample sizes (≤10). Second, most of the included studies used author-designed questionnaires, some of which were based on the PEQ. Third, satisfaction was not studied in all of the included studies. Fourth, in several studies patients' experiences with liners were assessed with test prostheses instead of definitive prostheses. Finally, in two studies the same population was researched.[12,13]
Given that prosthesis satisfaction is not only interpreted differently by researchers [1,2,6] but also operationalized differently in questionnaires, it is difficult to compare results of studies on prosthesis satisfaction. A comprehensive overview of factors that influence satisfaction with the prosthesis is currently missing. Such an overview will help clinicians to systematically assess these factors and target them to improve outcomes.
This systematic review aims to identify factors of influence on patient satisfaction with a definitive transtibial prosthesis, report satisfaction scores, present an overview of questionnaires used to assess satisfaction with the prosthesis, and examine how these questionnaires operationalize satisfaction.

Methods

This study is reported in accordance with the PRISMA guidelines. Ethical approval is not required for this is a systematic review of previously published studies.
Search Strategy
Six databases (PubMed, Embase, PsycInfo, CINAHL, Cochrane, and Web of Knowledge) were searched from their inception to Febuary , 2018. The search

strategy used for PubMed was based on terms related to (1) lower limb prosthesis, including "lower limb," "leg," "artificial limb," and "prosthesis"; and (2) patient satisfaction, including "patient satisfaction," "acceptance," "rejection," "satisfaction," and "dissatisfaction." Excluded were the terms "endoprosthesis,"," arthroplasty," "graft," "implant," and "breast." With the aid of an information specialist the search strategy for MEDLINE was designed: (leg OR lower limb) AND (prosthesis OR artificial limb) AND (patient satisfaction OR accept* OR reject* OR satisf* OR dissatisf*) NOT (endoprosthesis OR implant OR graft OR bypass OR breast). The search strategy was adapted for each of the databases accordingly.

Study selection

Studies were collected in a RefWorks database and duplicates (publications listed more than once) were removed. Two observers (JG, EB) independently assessed the titles and abstracts of the studies identified in the databases.

Inclusion criteria were as follows: a questionnaire was used to assess patient satisfaction with a definitive prosthesis; the transtibial amputation level was studied, or, in case of mixed samples, separate data were presented on transtibial amputee patients; age of (part of) the study population was >18 years and separate data were presented on this group; sample size was > 10; and studies were published in English, Dutch, or German.

Excluded were studies of interim or test prostheses, congress abstracts with no full text available, and all types of reviews. After title and abstract assessment, observer agreement was calculated (Cohen's Kappa and absolute agreement), and discrepancies in assessments were discussed between observers until consensus was reached. Full text studies included in the first round were assessed independently for inclusion and exclusion criteria by the same observers (JG, EB) and recorded on a predesigned form. Next, a consensus meeting took place to discuss the recorded studies. Double publications (studies using the same study population) were removed. Reference lists of included studies were checked for any relevant studies not identified in the database searches. The full text of these studies was assessed and inter-observer agreement was calculated.

The methodological quality of included studies was assessed independently by two authors (ES, EB) by means of a checklist based on the Methodology Checklist for Cross-Sectional/ Prevalence Studies of the Agency for Healthcare Research and Quality.[14] For longitudinal studies additional criteria from the Methodological Index of Non-Randomized Studies (Minors check list) were assessed.[15] When relevant data was missing or a mixed group of amputee patients was described in the study and no separate data on transtibial amputee patients were presented, we contacted the corresponding authors with the request to provide these data.

Factors associated with prosthesis satisfaction were extracted independently by 2 observers (ES, EB) and recorded on a predesigned form. These factors were categorized into 5 satisfaction domains: appearance of the prosthesis, properties of the prosthesis, fit of the prosthesis, use of the prosthesis, and aspects of the residual limb.

Questionnaires

Two observers (ES, a rehabilitation psychologist with 17 years of experience in rehabilitation care, and EB, a physiatrist with 18 years of experience in amputee

patient care) independently analyzed the questionnaires used in the studies regarding questions or combinations of questions that assessed prosthesis satisfaction. Questions that asked the patient to subjectively or emotionally evaluate the appearance and properties of the prosthesis or its fit and use were labeled as satisfaction questions. For example, the question "Rate how your prosthesis looks," with answering possibilities on a visual analogue scale anchored by "terrible/excellent," was labeled as a satisfaction question. If responses to a question were endorsed on a numerical scale, for example, "How many prostheses wore out?", this question was not labeled as a satisfaction question. Discrepancies in assessment of questions were discussed until consensus was reached.

Results

Search

A total of 1832 unique studies were identified for assessment after removal of duplicates from the search results. Thirteen studies were identified from the reference lists of the included studies (Figure 1). Cohen's Kappa as a measure for inter-observer agreement for title and abstract assessment was 0.793 , absolute agreement 98% . Eighty studies remained after the first assessment and full text of these studies was retrieved, in addition to the full text of studies identified from the reference lists. Sixty-seven studies were excluded (Figure 1).[10,13,16-76]

The assessment resulted in the final inclusion of 12 studies (Figure 1).[1,3-5,77-84]

Cohen's Kappa as a measure for inter-observer agreement of the full text assessment and selection was 0.39 (absolute agreement 67%).

Study descriptions and quality assessment

Most studies had a cross-sectional design. Two had a longitudinal design .[79,84]

Sample sizes varied from 14 to 581 participants, age ranged from 18 to 70 years and 60% to 100% was male. Participants were recruited from prosthetic centers, amputee patient groups, hospitals, medical services for armed forces service members, and registered charities (Table 1).[1,3-5,77-83]

One of the contacted authors responded to our request for additional data on transtibial amputee patients.[84]

Quality criteria that were met for ranging from 6 out of 10 to10 out of 10 (Table 2). The longitudinal studies [79,84] met 2 and 3 of the 8 additional Minors criteria (Table 2).

Overall satisfaction with the prosthesis was analyzed in 5 studies.[3,77,78,82,84] Van de Weg et al.[78] compared 2 overall satisfaction scores between groups of patients with different types of liners and found no significant differences between these patients.

Figure 1. Flow chart of paper assessment.

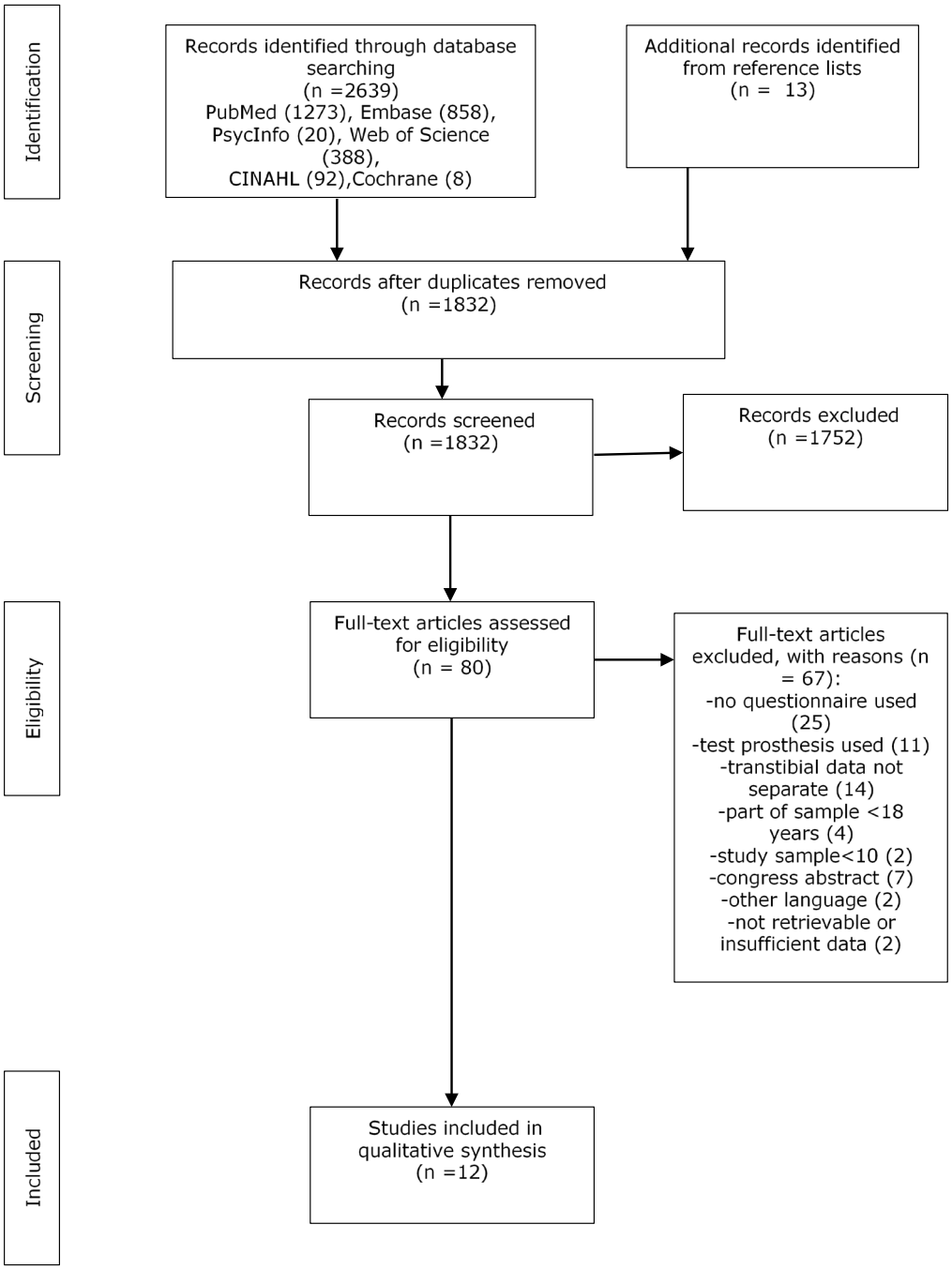

Table 1 Summary of participant characteristics from studies analyzing factors influencing patient satisfaction with transtibial prosthesis.

Study	Country	Recruitment	% Men (N)	TT(%)	Mean age ± sd (yrs)	Reason for amputation (%); level of amputation	TSA; PU (mn/ yrs)	HPU	Employment (%)	Questionnaire
Dillingham et al. 2001[4]	USA	Hospital	87% (78)	51%	33±11*	100% trauma; TF,TT,KD,A,F	TSA: 8±3yrs	nr	nr	Author designed questionnaire
Harness & Pinzur 2001[82]	USA	Hospital	77% (60)	100%	66±1	100% vascular; TT	PU: range 6-180mn	nr	nr	PEQ
vd Weg & vd Windt 2005[78]	NL	Limb fitting center Amputee group	60% (220)	100%	62±18	38% vascular 42% trauma 20% other; TT	PU: mean 17 ±16yrs	93% >6	27%	PEQ based
Berke et al. 2010[3]	USA	Armed forces service members:VV	100% (298)	75%	61	100% trauma; UL,TF,TT, F	TSA: mean 39 yrs	nr	79%	SPU
		OIF,OEF	97% (283)	56%	29				54%	
Gailey et al. 2010[5]	USA	Armed forces service members: VV	100% (178)	58%	61±3	100% trauma; HD,TF,KD,TT,A,F	TSA: mean 38±5 yrs	nr	80%	SPU
		OIF,OEF	98% (172)	54%	29±6	100% trauma; HD,TF,KD,TT,A,F	TSA: mean 3±1 yrs		57%	
Kark et al. 2011[1]	Australia	Amputee group	70% (20)	60%	62±12	15% vascular 85% trauma; TF,TT	TSA: 19±34yrs	nr	nr	PEQ
Ali et al. 2012[77]	Malaysia	Medical/engineering research center	100% (243)	100%	44±6	100% trauma; TT	PU:22±6yrs	12±3	nr	PEQ based
Webster et al. 2012[79]	USA	Department of Veterans Affairs medical centers, hospital, trauma center	100% (87)	60%	62±9	100% vascular; TF,TT	nr	nr	15%	TAPES
Cairns et al. 2014[83]	UK	Members of Murray Foundation, a registered charity in Scotland	69% (153)	67%	78% between 45-70 yrs	18% vascular, 15% diabetes 33% trauma 34% other; TF,KD,TT, HD,PF	PU: ≤9 to 69 yrs	≤8 to ≥12	nr	Author designed questionnaire
Samitier et al. 2014[81]	Spain	Hospital	88% (16)	100%	65±10	100% vascular; TT	PU:≥6mn	nr	nr	SATPRO
Sinah et al. 2014[80]	NL	Limb fitting center, rehabilitation center	88% (368)	76%	43±15	16% vascular/diabetes 76% trauma 8% other TF,KD,TT	TSA:13±10yrs PU:11±9yrs	10±4	59%	TAPES
Giesberts et al.[84]	Indonesia	Database limb fitting center	79% (11/14)	100%	37±10	13% (2/15) vascular 87% (13/15) trauma	TSA 12±12 PU:12 yrs (range 75 days-35 years)	t0: 13,2±4.2	nr	SCS PEQ Overall prosthesis satisfaction score (0-10)

*: age at time of amputation; A: ankle; F: (partial) foot; HD: hip disarticulation; HPU: hours of prosthesis use per day; KD: knee disarticulation; mn: months; nr: data not reported; NL: Netherlands; OIF/OEF: Veterans of Operation Iraqi Freedom/ Operation Enduring Freedom; PEQ: Prosthesis Evaluation Questionnaire; PU: prosthesis use; SATPRO: Satisfaction with Prosthesis Questionnaire; SCS: Socket Fit Comfort Score; SPU: Survey for Prosthetic Use; t0: fitting with modular socket system;TAPES: Trinity Amputation and Prosthesis Experience Scales; TF: trans-femoral; TSA: time since amputation; TT: trans-tibial; UK: United Kingdom; UL: upper limb; USA: United States of America; VV: Vietnam veterans; yrs: years

Table 2 Study quality assessment.

Quality criteria	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
Dillingham et al. 2001[4]	+	+	+	+	+	+	-	+	+	+	-	+								
Harnes & Pinzur 2001[82]	+	+	+	-	+	+	+	-	-	-	-	-								
Vd Weg & vd Windt 2005[78]	+	+	-	-	-	-	+	+	+	+	+	+								
Berke et al. 2010[3]	+	+	-	+	+	+	+	+	+	+	-	-								
Gailey et al. 2010[5]	+	+	+	+	+	+	+	-	+	-	-	-								
Kark et al. 2011[1]	+	+	+	-	+	+	+	-	+	+	-	-								
Ali et al. 2012[77]	+	+	-	-	+	+	+	-	-	-	-	+								
Cairns et al. 2014[83]	+	+	-	-	+	+	-	-	+	+	-	+								
Samitier et al. 2014[81]	+	+	+	-	+	-	+	-	+	-	-	-								
Sinah et al. 2014[80]	+	+	+	-	+	+	+	-	+	-	-	+								
Webster et al. 2012[79]	+	+	+	+	+	-	+	+	+	+	-	-	+	+	-	-	-	-	-	+
Giesberts et al.2017[84]	+	+	+	-	+	-	+	+	-	-	-	-	+	+	-	-	-	-	-	-
Sum	12	12	8	4	11	9	10	5	9	6	1	5	2	2	0	0	0	0	0	1

1. Is the source of information reported? 2. Were inclusion criteria reported? 3. Were exclusion criteria reported? 4. Was the time frame of recruitment reported? 5. Was the recruitment setting reported? 6. Were subjects consecutively recruited* or population based 7. Has the questionnaire been tested for measurement properties/unbiased assessment of study endpoints*? 8. Have participants been excluded from analysis? 9. Has confounding been assessed and controlled for, (subgroups analysis of multi variate analysis)? 10. Were missing data reported? 11. Were missing data imputed? 12. Was response rate reported? 13. Was there prospective collection of data?* 14. Was the follow-up period appropriate to the study aim?* 15. Was the loss to follow up less than 5%?* 16. Was there prospective calculation of study size?* 17. Was there an adequate control group?* 18. Were there contemporary groups?* 19. Was there baseline equivalence of groups?* 20. Was there adequate statistical analysis?*

*: Criteria for longitudinal studies

Overall satisfaction

A regression analysis demonstrated that male gender, paid work, a nonvascular reason for amputation, and a longer period of time since amputation were associated with somewhat higher satisfaction scores. Ali et al.[77] analyzed satisfaction with liners and found significantly higher overall satisfaction scores for Seal-in liner users. Berke et al. [3] reported mean overall satisfaction scores (range 0-10) in veterans and service members who lost limbs in the Vietnam conflict (7.3) or in the Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) conflicts (7.5). Harness et al. [82] found overall satisfaction to be associated with "appearance" (r =0.44), "residual limb health" (r=0.44), "less pain" (r=0.40), "ability to ambulate" (r=0.66), and "ability to make transfers" (r=0.36). Giesberts et al. [84] analysed satisfaction with the modular socket system in a longitudinal study using an overall prosthesis evaluation score, ranging from 0-10, with 0 equaling "not at all satisfied" and 10 equaling "very satisfied".

Mean visual analogue scale (VAS) scores (range 0-10) for overall satisfaction ranged from 6.9 [77] to 7.7,[84] and mean overall satisfaction sum scores (range 0-21) ranged from 11.0 to 12.0.[78] Mean overall satisfaction with liners (range 0-100) ranged from 63.1 for polyethylene liners to 83.1 for Seal-in liners.[77]

Appearance

Several studies described the percentage of patients satisfied with the appearance of their prostheses or reported satisfaction scores regarding appearance.[4,77,78,82,84] Harness et al.[82] found a positive association between overall satisfaction and appearance of the prosthesis (r=0.44). Two studies compared different prosthesis liners in relation to satisfaction with appearance. [77,78] Van de Weg et al.[78] found no significant differences regarding satisfaction with appearance of the prosthesis ("looks") between users of different liners. Ali et al.[77] found that patient satisfaction with appearance of the prosthesis was highest for Seal-in liner users. The operationalization of satisfaction with appearance of the prosthesis included the factors "appearance," "color," "touch/feel," "look(s)," "cosmetics," and "shape."[4,77,78,82-84]Giesberts et al. [84] found, no change in satisfaction with appearance over time using the PEQ, in patients using the modular socket system.

The PEQ was applied in 3 studies and uses an appearance scale to assess satisfaction.[1,82,84] This scale includes 5 questions: 1 on appearance of the prosthesis, 2 on damage done to clothing or prosthesis cover, and 2 on freedom in choice of clothing and shoes. PEQ-based questionnaires were used in 2 studies. One study included a question on cosmetic satisfaction with the prosthesis, a concept closely related to appearance, while the other study included a question on satisfaction with appearance.[77,78] The TAPES, used in 2 studies, includes 1 question regarding satisfaction with appearance.[79,80] This question is part of its Aesthetic Satisfaction Subscale. The other 2 questions of this subscale assess satisfaction with the shape and color of the prosthesis. In the Survey for Prosthetic Use (SPU), used in 2 studies, appearance is not assessed.[3,5] The Satisfaction with Prosthesis Questionnaire (SATPRO) was used in 1 study and includes 15 questions, 1 of which assesses satisfaction with the look of the prosthesis.[81] Two studies used author- designed questionnaires. Dillingham et al.[4] used 1 question to assess satisfaction with the appearance of the prosthesis. Cairns et al.[83] included a subscale on the aesthetics of

the prosthesis, another concept closely related to appearance. This subscale includes 3 questions assessing "color," "shape," and "feel/touch" of the prosthesis.

Properties of the prosthesis

Satisfaction with properties of the prosthesis was reported in 7 studies.[3-5,79,80,83,84] Sinha et al.[80] found that satisfaction with the weight of the prosthesis was significantly higher in transtibial amputee patients compared with transfemoral amputee patients. Webster et al.[79] found significantly lower levels of functional satisfaction in transtibial amputee patients compared with transmetatarsal amputee patients. No significant differences in satisfaction with functional and physical properties of the prosthesis were found between Vietnam veterans and OIF or OEF veterans in the study of Berke et al.[3] Another study found a prosthesis rejection rate of 18% in Vietnam veterans and 31% in OIF or OEF veterans.[5] The operationalization of satisfaction with functional and physical properties of the prosthesis included the factors "weight," "smell," "noise," "being waterproof," "durability," "reliability," "usefulness," "easy to clean," "ease of use," "works well regardless of the weather", "limitations imposed on clothing," "shoe choice (height and style)," "damage done to clothing," and "interaction of prosthesis cover with clothing and joint movement." [3-5,79,80,83,84]

Giesberts et al. [84] found a non-significant decline in PEQ scores over time when assessing satisfaction with sounds of the prosthesis. The PEQ includes 2 questions on satisfaction with properties of the prosthesis.[1,82] These questions assess the patients rating of "prosthesis weight" and "squeaking, clicking or belching sounds" made by the prosthesis. Two PEQ- based questionnaires also included satisfaction questions assessing the properties "sound" and "smell" of the prosthesis.[77,78] The Functional Satisfaction Subscale of the TAPES includes 3 questions on satisfaction with "weight," "usefulness," and "reliability" of the prosthesis.[79,80] The SPU has a satisfaction section with 3 questions on satisfaction with "smell," "sound," and "weight" of the prosthesis and a dissatisfaction section with questions on "lack of reliability" and "lack of functionality" of the prosthesis.[3,5] In the SATPRO, 4 of the 15 questions concern properties of the prosthesis. The scores on these questions are not analyzed on item level.[81] An author-designed questionnaire included 3 questions on factors affecting satisfaction with the cosmetic properties of prosthesis: "durability, "being waterproof," and "easy to clean." [83]

Fit

Dillingham et al.[4] reported on satisfaction with the fit and comfort of the prosthesis without using a between- group comparison. Other studies that examined the fit of the prosthesis did perform between-group comparisons of war veterans and included the variables employment, gender, marital status, reasons for amputation, years since amputation and mobility level. Three out of 4 studies found no significant differences between groups.[3,78,81] Ali et al.[77] found that the type of liner significantly influenced patient satisfaction with the fit of the prosthesis. Satisfaction with prosthesis fit and suspension was highest in Seal-in liner users, and satisfaction with prosthesis donning and doffing was highest in users of polyethylene foam liners.[77] The operationalization of satisfaction with fit included the factors "comfort," "fit", "donning and doffing," "suspension," "pistoning," "rotation," and "socket fit." [3,4,77,78,81,84]

Giesberts et al. found a significant decline (p 0,027) in satisfaction with comfort and pain over time using the Socket Fit Comfort Score (SCS) in patients using the modular socket system. [84] The Utility Scale of the PEQ includes 2 questions on satisfaction with the fit and comfort of the prosthesis; the latter is a concept closely related to fit.[1,82] In a PEQ-based questionnaire, 1 question was used to measure satisfaction with fit ("comfort to wear").[78] The TAPES has incorporated "fit" and "comfort" into 3 questions on prosthesis properties in a subscale assessing satisfaction.[79,80] The SPU includes 1 satisfaction question on "fit." [3,5] The SATPRO also includes 1 question on satisfaction with the comfort of the prosthesis.[81] The SCS assesses satisfaction with socket comfort while sitting, standing and walking, using a scale ranging from 0-10, with 0 being "most uncomfortable socket you can imagine" to 10 the "most comfortable socket fit". [84]

Aspects of the residual limb

Berke et al.[3] compared differences in satisfaction with the prosthesis between 3 groups of veterans with limb loss. It was found that Vietnam veterans had significantly less skin problems of the residual limb than OIF or OEF veterans, which positively affected their satisfaction with the prosthesis. Another study found overall satisfaction to be associated with residual limb health and less pain in the residual limb (r=0.4).[82] Giesberts et al. found a non-significant decline in residual limb health using the PEQ in patients using the modular socket system. [84] The operationalization of satisfaction with the residual limb included the factors "sweating/perspiration," "wounds," "irritation," "blisters," "pimples," "skin rash," "swelling," "pain," and "phantom pain." [1,3-5,79,80,82]

The PEQ includes a Residual Limb Health Scale containing 6 questions and a total of 10 questions on pain, 3 of which specifically assess pain in the residual limb.[1,82,84] Questionnaires based on the PEQ included several questions on different aspects of the residual limb that influence satisfaction, such as "sweating," "wounds," "irritation," "smell," and "pain." [77,78] The TAPES includes 1 question on residual limb pain.[79,80] The SPU includes 3 questions on aspects of the residual limb that impact satisfaction; these include "pain," "skin problems," and "sweating." [3,5] An author-designed questionnaire included questions on "skin irritation," "wounds," "perspiration," and "pain." [4]

Use of the prosthesis

In 2 studies differences between groups regarding satisfaction with prosthesis use were analyzed.[77,78] Users of polyethylene foam inserts were more satisfied than users of silicon liners or polyurethane liners while sitting or while walking on uneven terrain.[78] Users of Seal-in liners were more satisfied while "sitting," "walking," "walking on uneven terrain," and "walking on stairs" than users of silicone liners with a shuttle lock or polyethylene foam liners.[77] Harness et al.[82] analyzed factors associated with satisfaction with prosthesis use. Satisfaction with use was associated with the "ability to ambulate" and the "ability to transfer." Giesberts et al. [84] found no significant change in ambulation or prosthesis utility over time in patients fitted with the modular socket system. Another study found that satisfaction with walking with the prosthesis was higher in transtibial amputee patients than in transfemoral amputee patients.[1] The operationalization of satisfaction with use included

satisfaction with "sitting," "walking," "walking on uneven terrain," "walking up and down stairs," "ease of use," "daily use," and performance-based measures.[1,4,77,78,82-84]

The Ambulation Scale of the PEQ includes 8 questions, 1 of which assesses satisfaction while walking down the stairs.[1,82,84] The PEQ-based questionnaires included questions on satisfaction with prosthesis use in different circumstances, including "sitting," "walking," "climbing stairs," and "walking on uneven terrain." [77,78] In the SATPRO, 2 of the 15 questions assess satisfaction with prosthesis use.[81]An author-designed questionnaire assessed satisfaction with a question on "hours of prosthesis use." [4]

Table 3 Satisfaction scores and factors related to satisfaction grouped in 5 domains.

Author/ publication year	Statistics	Questionnaire Comparison	Appearance	Properties	Fit	Residual limb	Use
Dillingham et al. 2001 [4]	Scale mean range:0-100	Author designed	Appearance: 58.1	Weight: 58.1	Comfort: 43.2		Ease of use: 60.8
Harness & Pinzur 2001 [82]	Scale mean (sd),range :0-100	PEQ	Appearance: 73.3(2.4)			Residual limb health: 79.7(2.3)	Ambulation: 55.3(3.1) Transfer: 64.6(2.9)
	Regression analyses	Associations with overall satisfaction	Appearance: r=0.44*			Residual limb health: r=0.44* Less pain r=0.40*	Ability to ambulate: r= 0.66* Ability to transfer: r=0.36*
vd Weg & vd Windt 2005 [78]	Percentage (%) satisfied Chi square?	PEQ based Satisfied with liner Comparison of 3 liners: PEFI/ SL/ PUL	Looks: 67%/ 68%/ 66%		Fit: 69%/64%/68 % Donning and doffing:79%/ 77%/78%		Sitting: 88%/ 62%/ 59%* Walking: 70%/ 60%/ 54% Walking uneven terrain: 46%/ 25%/ 39%* Stairs: 54%/ 51%/ 45%
	Mean (sd), range: 0-10 ANOVA Mean(sd) range: 0-21 ANOVA	Overall satisfaction score 7.3(1.0)/ 7.0(2.1)/ 6.9(1.9) Satisfaction sum score 12.0(3.9)/ 11.3(5.0)/ 11.0(5.0)					
	Regression Analyses Satisfaction sum score	Males were more satisfied than females (b=2.6*). Working amputee patients were more satisfied than non- working (b=1.6*). Vascular amputee patients were less satisfied than other amputee patients (b=-1.7*). Patients amputated less than 10 years ago were less satisfied than patients with a more longstanding amputation (b=-1.9*)					

Berke et al. 2010 3	Percen-tage satis-fied with prosthe-sis Chi-square	SPU Comparison: VV/ (OIF, OEF) Overall satisfaction 7.3/ 7.5 (range 0-10)		Weight: 95%/94% Noise: 40%/ 48% Smell: 33%/ 39%	Fit: 91%/ 82% Socket comfort and fit: 76%/ 73%	Skin problems: 52%/ 72%* Sweating: 70%/ 57%	
Gailey et al. 2010 5	Percentage of devices rejected	SPU Comparison VV/ (OIF, OEF)		Mechanical Waterproof Rejection: 18%/ 31%			
Kark et al. 2011 1	Point-biserial correla tion	PEQ					Walking: Trans-femoral amputee patients were less satisfied than trans-tibial amputee patients: rpb = 0.50*
Ali et al. 2012 77	Mean VAS (range 0-100) ANOVA	PEQ-based Satisfaction with liners Comparison: SLS/ PFL/ SIL Overall satisfaction 75.9/ 63.1/ 83.1*	Cosmetic 69.1/ 73.3/ 83.1*		Fit: 79.6/ 64.8/ 87.1* Donning/doffing:71.4/ 79.7/ 57.2* Suspension: 81.7/ 55.2/ 93.7*		Walking: 72.8/ 65.2/ 84.7* Uneven-walking: 63.9/ 54.1/ 77.9* Climbing stairs: 68.8/ 60.8/ 80.6* Sitting: 68.8/ 76.4/ 79.4*
Webster et al. 2012 79	Mean scores	TAPES mean Functional scale range (5-25)		Functional satisfaction was lower in transtibial amputee patients (17.8) than in trans-metatarsal patients (21.4)*			
Cairns et al. 2014 83	Percentage of wearers reporting neutral or	Author designed Satisfaction with cosmesis	Colour: 59% Shape: 49% Touch: 57%	Waterproof of quality: 61%			Fit under clothing: 45% Natural bending of cosmesis: 58%

	dissatisfied opinion			Ability to keep clean:64 % Durability : 45%			Influence on prosthetic joint movement: 43%
Samitier et al. 2014 81	Mean (range 15-60) t-test	SATPRO: satisfied with suspension system Comparison: MFCL-2 / MFCL-3			Without VASS: 30.5/25.7 With VASS: 26.5/ 28.4		
Sinah et al. 2014 80	Regression analyses	TAPES		Weight: Trans-femoral amputee patients were less satisfied with weight than trans-tibial patients b=-.399*,			
Giesberts et al. 2017[84]		SCS (range 0-10), PEQ	Appearance score PEQ t1:81 t2:84	Sounds score PEQ t1:93 t2:81	Comfort SCS: t1:7.3±1.5 t2:7.0±1.3	Residual limb health score PEQ t1:79 t2:78	Utility score PEQ: t1:75 t2:74 Ambulation score PEQ: t1:74 t2:73

Table 4: Assessment of satisfaction questions in questionnaires.

Questionnaire	Domain, question	Single question or scale from guideline	Answer possibilities, ( ) question number	SQ[1]	SQ[2]
TAPES-R Please tick the box that represents the extent to which you are satisfied or dissatisfied with each of the different aspects of your prosthesis mentioned below:	Subscale Aesthetic satisfaction i Colour ii Shape iii Appearance Subscale Functional satisfaction iv Weight v Usefulness. vi Reliability vii Fit	Scale 3 items Scale 5 items	3-point scale: 1. Not satisfied 2. Satisfied 3. Very satisfied		

	viii Comfort				
TAPES-R Please circle the number (0-10) that best describes how satisfied you are with your prosthesis?	Overall satisfaction	question	Scale: 0 (not at all satisfied) -10 (very satisfied)		
SATPRO For each question, please circle the number that best describes your satisfaction with your prosthesis.	My prosthesis is **comfortable.** When I am in the presence of people other than my family, I **am at ease** wearing my prosthesis. My prosthesis is easy to clean. My prosthesis **works well** regardless of the weather. My prosthesis is **easy** to put on. There are chances that I will hurt myself with my prosthesis. **I find it easy** to move with my prosthesis. The repairs/adjustments to my prosthesis are done in reasonable time. My prosthesis will last me a long time. When I wear my prosthesis**, I can accomplish more** things than without it. I am **satisfied** with the look of my prosthesis. **I find it easy** to use my prosthesis with or without a walker/cane. **It was easy** to understand how to use my prosthesis. My prosthesis causes me physical pain or **discomfort.** In general, I am satisfied with my prosthesis.	No guideline	4-point scale for all items: 1. Totally agree 2. Rather agree 3. Rather disagree 4. Totally disagree	6 8 9 10 12	
PEQ Satisfaction questions (over the past four weeks)	1A. Rate **how happy** you have been with your current prosthesis. 16A Rate **how satisfied** you have been with your prosthesis. 16B Rate **how satisfied** you have been with how you are waking.	Three single questions	visual analogue scale anchored with: ”extremely unhappy/extremely happy” (1A) visual analogue scale anchored with: ”extremely dissatisfied/extremely satisfied”(16A, 16B)		
PEQ Well being scale (2 items) (over the past four weeks)	16C Rate **how satisfied** you have been with how things have worked out since your amputation.	Scale 2 questions	visual analogue scale anchored with: ”extremely dissatisfied/extremely satisfied” (16C)		16C
PEQ Utility scale (6 items) (over the past four weeks)	1B, **Rate the fit** of your prosthesis. 1C. **Rate the weight** of your prosthesis. 1D. **Rate your comfort** while standing when using your prosthesis.	Scale 8 questions	visual analogue scale anchored with: “terrible/excellent”(1B,1C,1D,2E,2I)		1B 1C 1D 2E 2H

	2E. **Rate your comfort** while sitting when using your prosthesis. 2G. **Rate** how **much energy** it took to use your prosthesis for as long as you needed it. 2H. **Rate the feel** (such as the temperature and texture) of the prosthesis (sock, liner, socket) on your residual limb (stump). 2I. **Rate the ease of putting on** (donning) your prosthesis.		visual analogue scale anchored with: "worst possible/best possible"(2H) visual analogue scale anchored with: "completely exhausting/not at all" (2G)		2I
PEQ Appearance scale (over the past four weeks)	3J. **Rate** how your prosthesis has **looked.** 4O. **Rate** your ability to wear the shoes (different height, styles) **you prefer**. 4P. **Rate** how limited your **choice of clothing** was because of your prosthesis	Scale 5 questions	visual analogue scale anchored with: "terrible/excellent"(3J) visual analogue scale anchored with: "cannot/ no problem" (4O) visual analogue scale anchored with: "worst possible/not at all"(4P)		3J 4O 4P
PEQ Sound scale (over the past four weeks)	3L. If it made any sounds in the past four weeks, rate how bothersome these sounds were to you.	Scale 2 questions	visual analogue scale anchored with: "extremely bothersome/not at all" (3L)		3L 4P
PEQ Residual Limb Health scale (over the past four weeks)	4R. Rate how smelly your prosthesis was at its worst. 5T. Rate any rash(es) that you got on your residual limb. 5U. Rate any ingrown hairs (pimples) that were on your residual limb 5V. Rate any blisters or sores that you got on your residual limb	Scale 6 questions	visual analogue scale anchored with: "extremely bothersome/not at all" (5T, 5U, 5V) visual analogue scale anchored with: "extremely smelly/not at all"(4R)		4R 5T 5U 5V
PEQ Pain question (over the past four weeks)	6C. How bothersome were these sensations in your phantom limb 7G. In the past four weeks how bothersome was the pain in your phantom limb 8J. How bothersome was the pain in your residual limb?		visual analogue scale anchored with: "all the time/never" (6C) extremely bothersome/extremely mild" (7G); "extremely bothersome/not at all" (8J)		6C 7G 8J
PEQ Ambulation scale	13D. Rate how you felt about being able to walk down stairs when using your prosthesis.		visual analogue scale anchored with: "cannot/no problem"(13D)		13D
PEQ Group 5 The following section asks about your satisfaction with particular	17E How satisfied are you with the person who fit your current prosthesis 17F. How satisfied are you with the training you have received on using your current prosthesis?	Three single questions about prosthetic care	visual analogue scale anchored with:" extremely dissatisfied/extremely satisfied"(17E, 17F, 17G)		17E 17F 17G

situations given that you have an amputation. Prosthetic care questions	17G. Overall, how satisfied are you with the gait and prosthetic training you have received since your amputation.				
PEQ Importance questions	19F. How bothersome is it when you sweat a lot inside your prosthesis (in the sock, liner, socket)? 20G. How bothersome to you is swelling in your residual limb (stump)? 20I. How bothersome is it to see people looking at you and your prosthesis?		visual analogue scale anchored with: "extremely bothersome/not at all"(19F,20G,20I)		19F 20G 20I
SPU section #7 Prosthetic satisfaction 7.1 For prosthetics that wore out (type: electronic, body-powered/mechanical, sports/ speciality)	a. How many prosthetics wore out? b. On average, how often have you had to replace your prosthesis?	No guideline	7.1: amount 7.2b: 4 different timeframes (less than yearly, every 1-2 years, every 3-5 years, every 6+years)	7.1a 7.1b	
SPU #7 7.2 For prosthetics that you do not like and stopped using (type: electronic, body-powered/mechanical, sports/ speciality)	a. How many were there? b. In general, what was the major reason why you stopped using each type of prosthesis?	No guideline	7.2: amount 7.2b: check all the boxes that apply (14 items)	7.2a 7.2b	
SPU #7 7.3. For prosthetics that you currently use, how true are the following statements?	a. My prosthesis **fits well**. b. The weight of my prosthesis is **manageable**. c. My prosthesis is **pain-free** to wear. d. My prosthesis **is easy to put on**. e. I am **bothered** with skin problems. f. I am **bothered** by noises from my prosthesis. g. I am **bothered** with smells from my h. I am **satisfied** with my prosthesis. i. I can cope with my prosthesis. j. I have adjusted to life with a prosthesis. k. I am interested in trying a different type of prosthesis on a trial basis. l. I want to change this current prosthesis to another type. m. I usually receive an appointment with my prosthetist within a reasonable amount of time (initial or repeat visits). n. I am satisfied with the training I initially received on how to use my prosthesis. o. I am satisfied with the training I received on how to maintain my prosthesis. p. I was fully informed about prosthetic equipment choices. q. I receive adequate information on new types of prostheses on a regular basis	No guideline	Select one box: Strongly Agree Agree Disagree Strongly Disagree (all items)	7.3i 7.3j 7.3k 7.3l 7.3m 7.3n 7.3o 7.3p 7.3q 7.3r	

	r. I had a role in choosing my prosthesis. s. I am **happy** with the comfort and fit of my socket. t. I am **bothered** with sweating inside my socket. u. I cannot wear my prosthesis because my **socket fits poorly**.				
SPU #7 7.4 Prosthetic service	a. In the last 5 years, did you feel that you were able to get a repair when you needed one? b. In the last 5 years, did you feel that you were able to get a replacement when you needed one? c. For your last prosthesis, how long did it take to get a new replacement (from when your physician placed the order until your new prosthesis was ready for the initial fitting)? d. How long do you think it should take to get a new replacement?	No guideline	Yes/no (7.4.a,7.4b) Check one of the 5 possibilities: 1-14 days, 2 - 4 weeks, up to 2 months, over 2 months, but less than 6 months, over 6 months (7.4c, 7.4d)	7.4a 7.4b 7.4c 7.4d	

1:Satisfaction question (SQ) according to the questionnaire guide lines, but we doubt that it is a SQ. 2 :not a satisfaction question(SQ) according to the questionnaire guide lines, but we consider it a SQ.

Discussion

Study aim

The analysis of the included studies revealed that a considerable number of transtibial amputee patients were not satisfied with their prostheses or aspects of their prostheses. Satisfaction with the prosthesis is a multidimensional construct that is affected by various factors. In the included studies several factors were found to influence satisfaction and dissatisfaction and the use of different operationalizations of satisfaction in the questionnaires makes comparison of outcomes between studies impossible.

Participants

Participants assessed in the included studies were predominantly physically active males who had undergone a traumatic amputation and who had a wide range in age and time since amputation.[1,3-5,77-84] In some studies participant characteristics were correlated. Armed forces service members, for example, were almost exclusively 30- to- 60- year- old males who were employed, had undergone traumatic amputations, and used their prostheses many hours per day.[3,4] Female amputee patients were underrepresented and outcome regarding appearance, comfort, and use of the prosthesis were not given separately for women.[1,3-5,78,80-84]

Overall satisfaction

Five studies assessed overall satisfaction with the prosthesis, which is the least specific evaluation of satisfaction.[3,77,78,82,84] Overall satisfaction scores give no insight into the specific aspects of satisfaction and offer no directions for improvement. The operationalization of overall satisfaction was associated with "appearance of the prosthesis" "residual limb health," "experiencing less pain," and "being able to ambulate and make transfers." [3,77,78,82] The scores on overall satisfaction suggest that there is considerable room for improvement (Table 3).

Appearance of the prosthesis

The use of the words "appearance," "look(s)," "cosmetics," and "aesthetics" in the questionnaires refer to the operationalization of appearance of the prosthesis and illustrates why it is difficult to draw comparisons between study outcomes. These words are similar in nature, for they all refer to the outward form/appearance of the prosthesis, but subtle semantic differences are nevertheless present. "Appearance" is the more neutral option, whereas "looks" and "aesthetics" refer to the appreciation of the appearance of the prosthesis. "Cosmetics," in turn, can also refer to the enhancement of the (normal) appearance. These words are not interchangeable, and differences in meaning may result in different interpretations of questions regarding appearance, thereby influencing the outcomes of the questionnaires.

The difference in the number of questions used in the scales of the questionnaires also makes it difficult to compare outcomes. The number of questions on satisfaction with appearance, for example, varied from 1 question in the SATPRO, 3 questions in the TAPES, and 5 questions in the PEQ, all with different scale ranges (Table 4). In addition, while most questionnaires assess satisfaction, only 1 assesses dissatisfaction with "reliability" and "functionality" of the prosthesis (SPU).[81] The low satisfaction scores on appearance of the prosthesis indicate that there is also room for (considerable) improvement (Table 3).

Properties of the prosthesis

One study reported on rejection rates of the prosthesis of 18% of Vietnam veterans and 31% of OIF/OEF veterans, predominantly because of dissatisfaction with properties of the prosthesis.[5] One study reported an increase of satisfaction with appearance and a decrease in satisfaction with sounds and utility of the prosthesis and a decrease of residual limb health over time.[84] In another study the mean satisfaction score regarding weight of the prosthesis was 58.1 (range 0-100).[4] Amputee patients with a more proximal amputation were less satisfied with the function and weight of the prosthesis than amputee patients with a more distal amputation, and transfemoral amputee patients were less satisfied while walking with the prosthesis than transtibial amputee patients.[1,79,81] As mentioned above, satisfaction in the domains "residual limb health" and "prosthesis use" is related to overall satisfaction.[82]

Again, considerable improvement is possible in these domains.

Prosthesis use

The PEQ assesses prosthesis use in different circumstances because of their possible influence on satisfaction. A person might be perfectly satisfied with the prosthesis while sitting but dissatisfied with the same prosthesis while walking on uneven terrain.[1,82] Thus satisfaction is also related to the kind of activity a person wants to do. Although most questionnaires include questions on prosthesis use, for instance regarding the distance walked, they do not include questions that measure the level of satisfaction with this particular distance.

Questionnaires

The reviewed studies used existing questionnaires, parts of existing questionnaires, adapted questionnaires, and author-designed questionnaires to measure prosthesis satisfaction. Various operationalizations were used in the questionnaires to assess aspects of satisfaction with a transtibial prosthesis. The reasons for choosing a particular operationalization were not explained in the questionnaire guidelines or discussed in the studies (Table 4). Furthermore, it was sometimes difficult to determine whether the questions assessed satisfaction or another construct. The following question illustrates this difficulty: "Over the past four weeks, rate how you felt about being able to walk down stairs when using your prosthesis." Answering possibilities were on a VAS anchored by "cannot" and "no problem" (PEQ 13D).[1,82] Because the answer indicates the patient's subjective/emotional evaluation of walking, this was considered to be a satisfaction question concerning prosthesis use. All factors that influence satisfaction were categorized into 5 different domains: appearance, properties, fit, residual limb, and use. The residual limb was mentioned in only 3 studies, despite the fact that it affects satisfaction with the prosthesis. Comparison of study outcomes was difficult due to different operationalizations of satisfaction in the questionnaires, differences in the phrasing of questions and choice of words, and differences in study objectives (Table 3, Table 4). In addition, the time frame studied also influences outcomes and was only evaluated in the PEQ. (Table 4).

Prosthesis satisfaction

The findings of this review indicate that it is important for researchers studying prosthesis satisfaction to motivate the use of a specific operationalization and

preferably cover all factors and domains influencing satisfaction (Table 4). This review provides an overview of factors that affect prosthesis satisfaction and can help researchers assess satisfaction during history taking, clinical examination, and prosthesis evaluation. At the same time, satisfaction is a subjective/emotional evaluation influenced by psychosocial factors that might change and vary over time. To enable research synthesis of prosthesis satisfaction in meta-analyses, researchers should be aware of the different operationalizations used in the questionnaires, for these impede comparisons of outcomes and calculation of effect sizes across studies.

Limitations of this review

The review was limited by the quality of the studies identified for inclusion. Many studies were excluded because they lacked specific data on transtibial amputee patients. In addition, only one author answered our request for additional data. We also excluded studies because of language restrictions and retrieval problems, thereby possibly excluding potential relevant studies. Studies included mainly employed males with traumatic amputations, which limits generalizability of findings to amputee patients with other characteristics. Patients were recruited from specific sources, which also limited generalizability. Finally, the diversity in questionnaires used and the different operationalizations of prosthesis satisfaction made pooling of quantitative data in a meta-analysis impossible.

Implications for future research

Ideally, prosthesis satisfaction should be systematically evaluated by means of an assessment of all known factors influencing satisfaction. The choice of a specific operationalization and questionnaire should be motivated. Furthermore, future research should take into account that prosthesis satisfaction is an emotional evaluation that is best assessed during a specific time frame, thereby respecting the dynamic aspects of satisfaction. Adhering to these principles will enhance comparability of future studies assessing prosthesis satisfaction and make meta-analysis and pooling of data possible.

Conclusion

Factors influencing patient satisfaction with a transtibial prosthesis are diverse and include appearance and properties (functional and physical) of the prosthesis, fit of the prosthesis, functional use of the prosthesis, and aspects of the residual limb. Relevance of certain factors seems to be related to specific amputee groups. Questionnaires assessing patient satisfaction use different operationalizations, making comparisons between outcomes of questionnaires impossible.

References

1. Kark L, Simmons A. Patient satisfaction following lower-limb amputation: the role of gait deviation. Prosthet Orthot Int 2011;35(2):225-233.
2. MohdHawari N, Jawaid M, MdTahir P, Azmeer RA. Case study: survey of patient satisfaction with prosthesis quality and design among below-knee prosthetic leg socket users. Disabil Rehabil Assist Technol 2017; 10: 868-874.
3. Berke GM, Fergason J, Milani JR, Hattingh J, McDowell M, Nguyen V. Comparison of satisfaction with current prosthetic care in veterans and service members from Vietnam and OIF/OEF conflicts with major traumatic limb loss. JRRD

2010;47(4):361-371.
4. Dillingham TR, Pezzin LE, MacKenzie EJ, Burgess AR. Use and satisfaction with prosthetic devices among persons with trauma-related amputations: a long-term outcome study. Am J Phys Med Rehabil 2001;80(8):563-571.
5. Gailey R, McFarland LV, Cooper RA, Czerniecki J, Gambel JM, Hubbard S. Unilateral lower-limb loss: Prosthetic device use and functional outcomes in servicemembers from Vietnam war and OIF/OEF conflicts. JRRD 2010;47(4):317-331.
6. Batbaatar E, Dorjdagva J, Luvsannyam A, Amenta P. Conceptualisation of patient satisfaction: a systematic narrative literature review. Perspect Public Health 2015;135(5):243-250.
7. Batbaatar E, Dorjdagva J, Luvsannyam A, Savino MM, Amenta P. Determinants of patient satisfaction: a systematic review. Perspect Public Health 2017;137(2):89-101.
8. Hills R, DipTP, Kitchen S. Toward a theory of patient satisfaction with physiotherapy: Exploring the concept of satisfaction. Physiother Theory and Pract 2007;23(5):243-254.
9. Gallagher P, Franchignoni F, Giordano A, MacLachlan M. Trinity amputation and prosthesis experience scales: a psychometric assessment using classical test theory and rasch analysis. Am J Phys Med Rehabil 2010;89(6):487-496.
10. Gallagher P, MacLachlan M. Development and psychometric evaluation of the Trinity Amputation and Prosthesis Experience Scales (TAPES). Rehabil Psychol 2000;45(2):130-154.
11. Richardson A, Dillon MP. User experience of transtibial prosthetic liners: A systematic review. Prosthet Orthot Int 2016; 1: 6-18.
12. Gholizadeh H, Abu Osman NA, Eshraghi A, Ali S, Arifin N, Wan Abas WA. Evaluation of new suspension system for limb prosthetics. Biomed Eng Online 2014;10; 13:1.
13. Gholizadeh H, Abu Osman NA, Eshraghi A, Ali S. The effects of suction and pin/lock suspension systems on transtibial amputees' gait performance. PLos ONE 2014;9(5),e94520:1-9.
14. Zeng X, Zhang Y, Kwong JS, Zhang C, Li S, Sun F, Niu Y, et al. The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: a systematic review. J Evid Based Med 2015;8(1):2-10.
15. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J.Methodological index for non-randomized studies (minors): development and validation of a new instrument. ANZ J Surg. 2003 Sep;73(9):712-716.
16. Alaranta H, Lempinen VM, Haavisto E, Pohjolainen T, Hurri H. Subjective benefits of energy storing prostheses. Prosthet Orthot Int 1994;18(2):92-97.
17. Åström I, Stenström A. Effect on gait and socket comfort in unilateral trans-tibial amputees after exchange to a polyurethane concept. Prosthet Orthot Int 2004;28(1):28-36.
18. Boutwell E, Stine R, Hansen A, Tucker K, Gard S. Effect of prosthetic gel liner thickness on gait biomechanics and pressure distribution within the transtibial socket. JRRD 2012;49(2):227-240.
19. Datta D, Harris I, Heller B, Howitt J, Martin R. Gait, cost and time implications for

changing from PTB to ICEX sockets. Prosthet Orthot Int 2004;28(2):115-120.
20. Datta D, Vaidya SK, Howitt J, Gopalan L. Outcome of fitting an ICEROSS prosthesis: views of trans-tibial amputees. Prosthet Orthot Int 1996;20(2):111-115.
21. Dudkiewicz I, Pisarenko B, Herman A, Heim M. Satisfaction rates amongst elderly amputees provided with a static prosthetic foot. Disabil Rehabil 2011;33(21-22): 1963-1967.
22. Arwert HJ, Van Doorn-Loogman MH, Koning J, Terburg M, Rol M, Roebroeck ME. Residual-limb quality and functional mobility 1 year after transtibial amputation caused by vascular insufficiency. JRRD 2007;44(5):717-722.
23. 1 Atherton R, Robertson N. Psychological adjustment to lower limb amputation amongst prosthesis users. Disabil Rehabil 2006;28(19):1201-1209.
24. Chadderton HC. Consumer concerns in prosthetics. Prosthet Orthot Int 1983;7(1):15-16.
25. Chen MC, Lee SS, Hsieh YL, Wu SJ, Lai CS, Lin SD. Influencing factors of outcome after lower-limb amputation: a five-year review in a plastic surgical department. Ann Plast Surg 2008;61(3):314-318.
26. Coffey L, Gallagher P, Desmond D. A prospective study of the importance of life goal characteristics and goal adjustment capacities in longer term psychosocial adjustment to lower limb amputation. Clin Rehabil 2014;28(2):196-205.
27. Dajpratham P, Tantiniramai S, Lukkapichonchut P, Kaewnaree S. Factors associated with vocational reintegration among the Thai lower limb amputees. J Med Assoc Thailand 2008;91(2):234-239.
28. Deans SA, McFadyen AK, Rowe PJ. Physical activity and quality of life: A study of a lower-limb amputee population. Prosthet Orthot Int 2008;32(2):186-200.
29. Gallagher P, Maclachlan M. Evaluating a written emotional disclosure homework intervention for lower-limb amputees. Arch Phys Med Rehabil 2002;83(10):1464-1466.
30. Gauthier-Gagnon C, Grise M, Potvin D. Enabling factors related to prosthetic use by people with transtibial and transfemoral amputation. Arch Phys Med Rehabil 1999;80(6):706-713.
31. Kegel B, Carpenter ML, Burgess EM. A survey of lower-limb amputees: prostheses, phantom sensations, and psychosocial aspects. Bull Prosthet Res 1977;10(27):43-60.
32. Legro MW, Reiber GD, Smith DG, Del Aguila M, Larsen J, Boone D. Prosthesis evaluation questionnaire for persons with lower limb amputations: Assessing prosthesis-related quality of life. Arch Phys Med Rehabil 1998;79(8):931-938.
33. Sapp L, Little CE. Functional outcomes in a lower limb amputee population. Prosthet Orthot Int 1995;19(2):92-96.
34. Van der Linde H, Hofstad CJ, Geertzen JH, Postema K, Van Limbeek J. From satisfaction to expectation: the patient's perspective in lower limb prosthetic care. Disabil Rehabil 2007;29(13):1049-1055.
35. Magnusson L, Ramstrand N, Fransson EI, Ahlström G. Mobility and satisfaction with lower-limb prosthesis and orthoses among users in Sierra Leone: a cross-sectional study. J Rehabil Med 2014; 46:438-446.36. Jarl G, Heinemann AW, Lindner HY, NorlingHermansson LM. Cross-Cultural Validity and Differential Item Functioning

of the Orthotics and Prosthetics Users' Survey with Swedish and United States Users of Lower-Limb Prosthesis. Arch Phys Med Rehabil 2015;96(9):1615-1626.
37. Raschke SU, Orendurff MS, Mattie JL, et al. Biomechanical characteristics, patient preference and activity level with different prosthetic feet: a randomized double-blind trial with laboratory and community testing. J Biomech 2015;48(1):146-152.
38. Sinha R, van den Heuvel WJ, Arokiasamy P, van Dijk JP. Influence of adjustments to amputation and artificial limb on quality of life in patients following lower limb amputation. Int J Rehabil Res. 2014;37(1):74-79.
39. Mohd Hawari N, Jawaid M, Md Tahir P, Azmeer RA. Case study: survey of patient satisfaction with prosthesis quality and design among below-knee prosthetic leg socket users. Disabil Rehabil Assist Technol. 2017 Nov;12(8):868-878.
40. Ali S, Abu Osman NA, Eshraghi A, Gholizadeh H, AbdRazak NAB, Wan Abas WABB. Interface pressure in transtibial socket during ascent and descent on stairs and its effect on patient satisfaction. Clin Biomech 2013;28(9-10):994-999.
41. Coleman KL, Boone DA, Laing LS, Mathews DE, Smith DG. Quantification of prosthetic outcomes: elastomeric gel liner with locking pin suspension versus polyethylene foam liner with neoprene sleeve suspension. JRRD 2004;41(4):591-602.
42. Gholizadeh H, Abu Osman NA, Eshraghi A, Ali S, Saevarsson SK, Wan Abas WA. Transtibial prosthetic suspension: less pistoning versus easy donning and doffing. JRRD 2012;49(9):1321-1330.
43. Hachisuka K, Dozono K, Ogata H, Ohmine S, Shitama H, Shinkoda K. Total surface bearing below-knee prosthesis: Advantages, disadvantages, and clinical implications. Arch Phys Med Rehabil 1998;79(7):783-789.
44. Selles RW, Janssens PJ, Jongenengel CD, Bussmann JB. A randomized controlled trial comparing functional outcome and cost efficiency of a total surface-bearing socket versus a conventional patellar tendon-bearing socket in transtibial amputees. Arch Phys Med Rehabil 2005;86(1):154-161.
45. Eshraghi A, Abu Osman NA, Karimi MT, Gholizadeh H, Ali S, Wan Abas WA. Quantitative and qualitative comparison of a new prosthetic suspension system with two existing suspension systems for lower limb amputees. Am J Phys Med Rehabil 2012;91(12):1028-1038.
46. Horne CE, Neil JA. Quality of life in patients with prosthetic legs: a comparison study. JPO 2009;21(3):154-159.
47. Boldingh EJ, Van Pijkeren T, Wijkmans DW. A study on the value of the modified KBM prosthesis compared with other types of prosthesis. Prosthet Orthot Int 1985;9(2):79-82.
48. Ali A, Abu Osman NA, Abd Razak NA, Hussain S, Wan Abas WAB. The effect of dermo and Seal-in X5 prosthetic liners on pressure distributions and reported satisfaction during ramp ambulation in persons with transtibial limb loss. Eur J Phys Rehabil Med 2015;159(1):31-37.
49. Morgan SJ, McDonald CL, Halsne EG, Cheever SM, Salem R, Kramer PA, Hafner BJ. Laboratory- and community-based health outcomes in people with transtibial amputation using crossover and energy-storing prosthetic feet: A randomized crossover trial. PLoS One. 2018 Feb 7;13(2):e0189652. doi: 10.1371/journal.pone.0189652. eCollection 2018.

50. Desmond D, Gallagher P, Henderson-Slater D, Chatfield R. Pain and psychosocial adjustment to lower limb amputation amongst prosthesis users. Prosthet Orthot Int 2008;32(2):244-252.
51. Gunawardena NS, Seneviratne RA, Athauda T. Prosthetic outcome of unilateral lower limb amputee soldiers in two districts of Sri Lanka. JPO 2004;16(4):123-129.
52. Akarsu S, Tekin L, Safaz I, Goktepe AS, Yazicioglu K. Quality of life and functionality after lower limb amputations: comparison between uni- vs. bilateral amputee patients. Prosthet Orthot Int 2013;37(1):9-13.
53. Coffey L, Gallagher P, Horgan O, Desmond D, MacLachlan M. Psychosocial adjustment to diabetes-related lower limb amputation. Diabet Med 2009;26(10):1063-1067.
54. Bilodeau S, Hebert R, Desrosiers J. Lower limb prosthesis utilization by elderly amputees. Prosthet Orthot Int 2000;24(2):126-132.
55. Murray C, Fox J. Body image and prosthesis satisfaction in the lower limb amputee. Disabil Rehabil 2002;24(17):925-931.
56. Karmarkar AM, Collins DM, Wichman T, Franklin A, Fitzgerald SG, Dicianno BE. Prosthesis and wheelchair use in veterans with lower-limb amputation. JRRD 2009;46(5):567-576.
57. Legro MW, Reiber G, Del Aguila MD, Ajax MJ, Boone DA, Larsen JA. Issues of importance reported by persons with lower limb amputations and prostheses. JRRD 1999;36(3):155-163.
58. Zidarov D, Swaine B, Gauthier-Gagnon C. Quality of life of persons with lower-limb amputation during rehabilitation and at 3-month follow-up. Arch Phys Med Rehabil 2009;90(4):634-645.
59. Fisher K, Hanspal R. Body image and patients with amputations: does the prosthesis maintain the balance? Int J Rehabil Res 1998;21(4):355-363.
60. Matsen SL, Malchow D, Matsen FA. Correlations with patients' perspectives of the result of lower-extremity amputation. J Bone Joint Surg Am 2000;82-A(8):1089-1095.
61. Pezzin LE, Dillingham TR, Mackenzie EJ, Ephraim P, Rossbach P. Use and satisfaction with prosthetic limb devices and related services. Arch Phys Med Rehabil 2004;85(5):723-729.
62. Roth EV, Pezzin LE, McGinley EL, Dillingham TR. Prosthesis use and satisfaction among persons with dysvascular lower limb amputations across postacute care discharge settings. PMR 2014;6(12):1128-1136.
63. Buijk CA. Use and usefulness of lower limb prostheses. Int J Rehabil Res 1988;11(4):361-367.
64. Christ O, Jokisch M, Preller J, Beckerle P, Wojtusch J, Rinderknecht S. User-centered prosthetic development: comprehension of amputees' needs. Conf Proc IEEE Eng Med Biol Soc 2012; 2012:1929-1932.
65. Gallagher P, Maclachlan M. Adjustment to an artificial limb: a qualitative perspective. J Health Psychol 2001;6(1):85-100.
66. Durmus D, Safaz I, Adıgüzel E, et al. The relationship between prosthesis use, phantom pain and psychiatric symptoms in male traumatic limb amputees. Compr Psychiatry 2015; 59:45-53.

67. Moustapha A, Sagawa Junior Y, Watelain E, Thevenon A. Epidemiological cross-sectional survey of outcome in lower-limb amputees in the Nord-Pas de Calais region. Ann Phys Rehabil Med 2010;53: e22.
68. Safari MR, Tafti N, Aminian G. Socket interface pressure and amputee reported outcomes for comfortable and uncomfortable conditions of patellar tendon bearing socket: A pilot study. Assist Technol 2015;27(1):24-31.
69. Kuret Z, Burger H. Quality of life in lower limb amputees. Prosth Orthot Int 2015;39 SUPPL. 1(434-).
70. Magnosson L. Variables associated with patients' satisfaction with low cost technology prosthetic and orthotic devices and service delivery in Malawi and Sierra Leone. Prosth Orthot Int 2015;39 SUPPL. 1(76-).
71. Posada AM, Lugo LH, Plata JA, Castaño A, López JM. Patients' perspectives on lower limb amputation outcomes. Prosth Orthot Int 2015;39 SUPPL. 1 (230-).
72. Kangkasomboon T, Assarut N, Sakaew T, Gatephong W, Phukitviraskul P, Kehasuwon W. Self-image and attitude on prosthetic cosmetic cover in lower limb amputee in Thailand. Prosth Orthot Int 2015;39 SUPPL. 1 (549-550).
73. Vazvani HG, Yahyavi E, Eshraghi A, et al. Clinical assessment of a new prosthetic suspension system. Prosth Orthot Int 2015;39 SUPPL. 1 (323-).
74. Vance RL, Gallagher P, O'Keeffe F, Desmond D, Coen R, Ryall N. The impact of cognition on physical and psychosocial outcomes at discharge from a lower limb prosthetic rehabilitation programme. Prosth Orthot Int 2015;39 SUPPL. 1 (545-).
75. Migaou Miled H, Ben Brahim H, HadjHassine Y, et al. Tunisian lower limb amputees and satisfaction towards their prosthesis: About 74 cases. Ann Phys Rehabil Med 2016;59S: e31-e32.
76. Christ O, Beckerle P, Rinderknecht S, Vogt J. Usability, satisfaction and appearance while using lower limb prostheses: Implications for the future. Neurosci Lett 2011;500: e50.
77. Ali S, Abu Osman NA, Naqshbandi MM, Eshraghi A, Kamyab M, Gholizadeh H. Qualitative study of prosthetic suspension systems on transtibial amputees' satisfaction and perceived problems with their prosthetic devices. Arch Phys Med Rehabil 2012;93(11):1919-1923.
78. van de Weg FB, van der Windt DAWM. A questionnaire survey of the effect of different interface types on patient satisfaction and perceived problems among trans-tibial amputees. Prosthet Orthot Int 2005;29(3):231-239.
79. Webster JB, Hakimi KN, Williams RM, Turner AP, Norvell DC, Czerniecki JM. Prosthetic fitting, use, and satisfaction following lower-limb amputation: a prospective study. JRRD 2012;49(10):1493-1504.
80. Sinha R, van den Heuvel WJ, Arokiasamy P. Adjustments to amputation and an artificial limb in lower limb amputees. Prosthet Orthot Int 2014;38(2):115-121.
81. Samitier CB, Guirao L, Costea M, Camós J, Pleguezuelos E. The benefits of using a vacuum-assisted socket system to improve balance and gait in elderly transtibial amputees. Prosthet Orthot Int 2016;40(1):83-88.
82. Harness N, Pinzur MS. Health related quality of life in patients with dysvascular transtibial amputation. Clin Orthop Relat Res 2001;(383):204-207.

83. Cairns N, Murray K, Corney J, McFadyen A. Satisfaction with cosmesis and priorities for cosmesis design reported by lower limb amputees in the United Kingdom: instrument development and results. Prosthet Orthot Int 2014;38(6):467-473.
84. Giesberts B, Ennion L, Hjelmstrom O, Karma A, Lechler K, Hekman E, Bergsma A. The modular socket system in a rural setting in Indonesia. Prosthet Orthot Int. [Epub ahead of print].

Chapter 5

Resilience in patients with amputation because of Complex Regional Pain Syndrome type I

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J Bone Joint Surg Am. 2014 Jun 4;96(11):930-934

Abstract

*Purpose***:** Although controversial, an amputation for longstanding and therapy-resistant
Complex Regional Pain Syndrome Type I (CRPS-I) may improve quality of life and pain intensity. Resilience, the way people deal with adversity in a positive way may be related to these positive outcomes. This study focused on the relationship between resilience and postamputation outcomes, i.e. quality of life, pain and recurrence of CRPS-I and psychological distress. *Method***:** Twenty-six patients with an amputation related to CRPS-I filled in the Connor Davidson Resilience Scale (CD-RISC), World Health Organisation – Quality of life Assessment (WHOQOL-Bref) and the Symptom Checklist-90 Revised (SCL-90-R). An interview was conducted and a physical examination performed. Results were compared with reference groups from literature and a control group from the outpatient rehabilitation clinic at our medical center.*Results***:** Resilience correlated significantly with all domains of the WHOQOL-Bref (r ranged from 0.41 to 0.72) and negatively with all domains of the SCL-90-R (r ranged from 0.39 to 0.68). Patients with an amputation because of CRPS-I have higher scores on resilience and quality of life than the control group. Resilience was lower in patients who reported CRPS-I symptoms compared to those who did not. *Conclusions***:** The results confirmed our hypothesis that patients with an amputation because of CRPS-I who have a higher resilience also have a higher quality of life and experience lower psychological distress. The prognostic value of resilience in this patient group requires further research

Introduction

Pain and swelling following a seemingly minor injury of wrist or ankle, do not recover in some patients within a normal timeframe. When pain intensifies and other symptoms occur and worsen (e.g. changes in sweating, colour or nail and hair growth) Complex Regional Pain Syndrome type I (CRPS-I) is likely to be present.[1] Guidelines offer evidence based treatment options for CRPS-I such as medication, physical therapy and occupational therapy.[2] However, not all patients respond to these therapies and in some patients CRPS-I may further develop into a dysfunctional limb with uncontrollable pain or life-threatening infection. [3-5] Sometimes a patient requests an amputation of the affected limb as a last resort. [6, 7]
Amputation for longstanding and therapy-resistant CRPS-I is controversial and a rare intervention.[8] Primarily, the aim of the amputation is to increase quality of life and mobility of the patient but also to decrease pain intensity. Outcome variables after an amputation such as quality of life have been infrequently reported.[8] Previously, there was insufficient evidence that amputation positively contributes to the treatment of CRPS-I, with just a few published case studies with positive outcomes.[2, 7, 9, 10] Guidelines warn against amputation and the risk of recurrence of the syndrome due to their referral to one or two larger studies with predominantly negative outcomes. [5,11-13] A systematic review on CRPS-I and amputation could not find enough evidence for or against amputation [8] Results

from our recent study in a group of 21 patients who had an amputation because of longstanding and therapy-resistant CRPS-I did show an overall improvement of life in general and improvements in pain intensity, quality of life, mobility, use of a prosthesis and job or study enrolment.[6] It is unknown why patients from this study have better results than most other patients described in literature.[6, 8] Patients faced physical disability and severe pain often several years prior to the amputation. After the amputation they seem to "bounce back" beyond what could be expected according to literature.
The ability to bounce back in times of adversity, including physical stress, is called resilience.[14] Resilience is defined as "the process of adapting well in the face of adversity, trauma, tragedy, threats, or even significant sources of stress — such as family and relationship problems, serious health problems, or workplace and financial stressors".[15] It represents a person's qualities that enable that person to thrive in the face of adversity.[16] In patients with traumatic amputations psychological recovery and acceptance of limb loss are positively influenced, not only by social support or medical care, but also by higher resilience.[17] Resilience may, in part, explain why patients are able to increase quality of life after amputation. Insight in resilience of patients with a limb amputation because of CRPS-I could guide patient selection and give reason for offering patients a program to increase their resilience before and after amputation.
Based on the results from our previous study on quality of life, we hypothesised that higher scores on quality of life and participation in daily life may be correlated with higher resilience. The aim of this study was to analyse resilience and post amputation outcome (CRPS-I symptoms, quality of life, psychological distress and participation in daily life) and to analyse how resilience relates to these outcome variables in patients with an amputation because of CRPS-I.

Methods

Participants and procedures
Patients with a request for amputation were referred to our outpatient clinic by their consultant in rehabilitation medicine, their general practitioner, or they came on their own initiative. Our rehabilitation medicine outpatient clinic is situated in a university based medical centre which serves as one of the referral clinics for people with longstanding and therapy-resistant CRPS-I in our country. Upon referral the patient was independently assessed by a consultant in rehabilitation medicine, vascular surgeon, physical therapist and psychiatrist or psychologist. CRPS-I was diagnosed according to the criteria of the International Association for the Study of Pain (IASP) and the criteria of Bruehl.[18,19] Patients were considered eligible for amputation if other diagnoses were ruled out, if (all) therapies for CRPS-I advised in guidelines were tried but failed (including infection and wound therapy) and if quality of life was experienced as poor and participation in daily life activities was hindered excessively. In a multidisciplinary meeting the health care professionals discussed the pros and cons of an amputation together, and then later discussed these with the patient.
All patients (n=27) who underwent elective amputation because of CRPS-I at our centre between 2000 and 2011 were contacted to participate in this cross-sectional

explorative study. After agreement on participation, patients were sent more information about the study, questionnaires and an informed consent form. Patients with insufficient knowledge of the Dutch language or younger than 18 years were excluded from the study. The study included several questionnaires, a semi-structured interview and a physical examination. The medical ethical committee approved the research (METc 2009/117).

Questionnaires

Resilience was assessed with a Dutch version of the Connor-Davidson Resilience Scale (CD-RISC), a 25 item self-report measure that was developed to quantify current resilience.[16, 20] The score ranges from 0 to 100 with higher scores indicating a better resilience.

Quality of life was evaluated with the World Health Organization - Quality of life Assessment (WHOQOL-Bref), a 26 item questionnaire covering four domains: physical health, psychological health, social relationships and environment.[21] The scores range in each domain from 4 to 20; higher scores indicate better quality of life in a certain domain. The results of the WHOQOL-Bref of 21 patients included in this study have been described previously.[6]

Psychological distress was assessed with the Symptom Checklist-90 Revised (SCL-90-R).[22] The SCL-90-R assesses self-reported psychological distress and multiple aspects of psychopathology. It consists of 90 questions in eight dimensions of psychological distress: anxiety, agoraphobia, depression, somatisation, insufficiency, sensitivity, hostility and insomnia. Patients report to which extent the symptoms of the checklist were present in the week preceding the completion of the questionnaire. Higher scores in the SCL-90-R indicate more problems. It can be used with single dimensions but also as a total psycho neuroticism. All questionnaires have five point Likert scales, scoring from 0 to 4 (CD-RISC) or 1 to 5 (WHOQOL-Bref and SCL-90-R).

Interview and physical examination

A visit to the patient for an interview and physical examination by a psychologist and a physician was scheduled in a hospital close to or at the patient's home. Main results from the interview have been published.[6] Patients were asked if they still experienced CRPS-I related symptoms, stump pain and phantom pain in the two weeks before the visit. Stump pain and phantom pain were recorded on a visual analogue scale (VAS) in millimetres (mm).

After the interview, the physician performed a physical examination of the limbs for (recurrence of) CRPS-I [19] and the psychologist checked all questionnaires for missing answers and asked patients to fill in the missing answers.

Analysis

The results of the CD-RISC and WHOQOL-Bref questionnaires were compared with unpublished data from a control group from our outpatient rehabilitation clinic. The control group exists of chronic pain patients selected from patients seen by the psychologist from our rehabilitation clinic between 2008 and 2013 (n ¼111; male 34%, mean age 45.9 years SD 13.4 years, female 66%, mean age 40.0 years SD 13.2 years). Patients in this control group experienced chronic pain (46 weeks) and social and psychological factors played a considerable role in maintaining the health related complaints. The results of the CD-RISC were also compared with those of a

non help-seeking general population sample (n=577) and primary care outpatients (n=139) in the United States of America.[16] WHOQOL-Bref scores were additionally compared with scores found in the general Dutch population (n=218, male 41%, mean age 37.5 years SD 7.6, female 59%, mean age 37.4 SD 8.2). [23] SCL-90-R scores were compared with norm values for the Dutch population (n=2394, male: female 50%:50%, mean age 41.1 years SD 14.5) and for patients with chronic pain (n=2461, male: female 32%:68%, mean age 46.2 years SD 15.4).[22] Comparisons were made using Confidence Interval Analysis (CIA 2.2.0 University of Southampton).[24] Associations between resilience and the other outcome parameters were analysed. Non-parametric correlations (Spearman's ρ) and Mann Whitney U tests were used.
PASW Statistics version 18 for Windows was used for data analysis. Results are significant at $p \leq 0.05$.

Results

Patient characteristics
Of the 27 contacted patients, 26 agreed to participate: 23 women and three men, median age 44 years (Interquartile range (IQR): 34; 48). Patients underwent amputation between May 2000 and May 2010. Median duration of CRPS-I was 5.5 years (IQR: 3; 10). Median interval between amputation and study was 56 months (IQR: 25; 69). Twenty patients underwent amputation of a lower extremity (LE) and six patients of an upper extremity (UE). No patients were excluded. Previous failed therapies included combinations of e.g.: physical therapy including pain exposure physical therapy [25], occupational therapy, manipulation, sympathetic blocks or sympathectomy, medicine such as morphine anti-anxiety agents and dimethylsulfoxide cream (50%)[12]. Before amputation patients generally experienced their quality of life as poor and often referred to their affected limb as "paw" , "canon" or "obstacle".
Measures
The mean CD-RISC was significantly higher than that of the control group at our outpatient rehabilitation clinic (Table 1). CDRISC scores were significantly lower compared to values for a USA non help-seeking general population sample and similar to patients seeking primary care (Table 1) [16].

Table 1. Mean and standard deviation for CD-RISC and WHOQOL-Bref domain scores of patients who had a limb amputation because of longstanding therapy-resistant Complex Regional Pain Syndrome type I (CRPS-I) compared to reference and control groups.

	CRPS-I	**Reference and control groups**	**Difference (95% CI)**
CD-RISC	73.3(11.7)	*Non help seeking*[16]	
		80.4(12.8)	7.1 (2.1; 12.1)*
		Primary care [16]	
		71.8 (18.4)	-1.5 (-8.9; 5.8)
		Outpatient rehabilitation clinic	-13.1 (7.9; 18.4)*
		60.2 (12.3)	
WHOQOL-Bref domains		*Dutch norm values* [23]	
Physical	12.7 (3.6)	15.2 (2.6)	2.6 (1.4; 3.7)*
Psychosocial	14.4 (2.7)	14.4 (2.0)	0.1 (-0.9; 0.8)
Social	15.1(3.7)	15.4 (2.9)	0.3 (-0.9; 1.6)
Environment	13.9(2.8)	15.8 (2.0)	1.9 (1.0; 2.8)*
		Outpatient rehabilitation clinic	
Physical		9.8(2.4)	2.9 (-4.0; -1.7)*
Psychosocial		12.8(2.3)	1.6 (-2.6; -0.6)*
Social		13.7(3.5)	1.4 (-2.9; 0.2)
Environment		13.6(2.2)	0.4 (-1.4; 0.7)

CD-RISC: Connor-Davidson Resilience Scale; reference values taken from Development of a new resilience scale: the Connor-Davidson Resilience Scale (CD-RISC) [16]. WHOQOL-Bref: World Health Organization Quality of Life-BREF questionnaire; reference values taken from Quality of life and psychopathology: Investigations into their relationship [23]. Control group: outpatient rehabilitation clinic: results from patients with chronic pain (46 weeks duration). CI: Confidence interval; *p≤0.05.

WHOQOL-Bref.

Sixteen patients (62%) reported a good or very good quality of life; four patients (15%) reported good nor bad and six patients (23%) reported a poor or very poor quality of life. Patients scored significantly higher (=better) on the physical and psychosocial domain compared to patients in our control group (Table 1). Patients scored significantly lower on the physical and environmental domain compared to Dutch norm values.

SCL-90-R.

Patients scored significantly higher (=worse) on depression, somatisation, insufficiency, insomnia and psycho neuroticism compared to the Dutch norm values (table 2)[22]. However, they scored similar to Dutch norm values for chronic pain patients)[22].

Table 2. Mean (SD) SCL-90-R domain scores of patients who had limb amputation because of longstanding therapy-resistant Complex Regional Pain. Syndrome type I (CRPS-I) compared with Dutch norm values.

	CRPS-I	**Dutch norm values**	**Difference (95% CI)**	**Chronic Pain**	**Difference (95% CI)**
Anxiety	13.4 (5.4)	12.8 (4.4)	−0.5 (−2.2; 1.2)	15.4 (6.3)	2.1 (−0.3; 4.5)
Agoraphobia	8.7 (3.1)	7.9 (2.3)	−0.9 (−1.8; 0.0)	9.1 (4.0)	0.3 (−1.2; 1.9)
Depression	26.1 (12.0)	21.6 (7.6)	−4.5 (−7.5; −1.6)*	28.4 (11.4)	2.3 (−2.1; 6.7)
Somatization	22.6 (8.6)	16.7 (5.3)	−5.9 (−8.0; −3.9)*	24.8 (7.9)	2.2 (−0.9; 5.3)
Insufficiency	16.9 (6.0)	12.6 (4.3)	−4.3 (−5.9; −2.6)*	17.9 (6.4)	0.9 (−1.5; 3.4)
Sensitivity	25.5 (8.9)	24.1 (7.6)	−1.4 (−4.4; 1.5)	25.2 (9.1)	−0.3 (−3.8; 3.2)
Hostility	7.1 (1.5)	7.2 (2.1)	0.1 (−0.7; 1.0)	8.2 (3.1)	1.1 (−0.1; 2.3)
Insomnia	7.0 (3.9)	4.5 (2.2)	−2.5 (−3.4; −1.6)*	7.4 (3.7)	0.5 (−1.0; 1.9)
Psychoneuro-ticism	138.7 (46.0)	118.3 (32.4)	−20.4 (−33.0;-7.8)*	148.6 (45.5)	9.9 (−7.7; 27.5)

SCL-90-R: Symptom Checklist 90 Revised; Chronic Pain: Normal values for chronic pain patients. Reference values taken from Symptom Checklist [22]. *p<0.05; CI: confidence interval.

Interview and physical examination
Fifteen patients (56%) reported recurrence of CRPS-I-like symptoms. Twenty-three patients (88%) reported stump pain (median VAS score 31mm; IQR: 6; 63) and 20 patients (77%) reported phantom pain (median VAS score 25mm; IQR: 2; 51). Five patients (19%) met Bruehl's criteria [19] for recurrence of the syndrome in the stump and two patients (8%) for recurrence in another limb.
Associations
The CD-RISC correlated positively with all domains of the WHOQOL-Bref (ρ ranged from 0.41 to 0.72) and negatively with all domains of the SCL-90-R (ρ ranged from -0.39 to -0.68) (table 3).
A positive, though not significant association (ρ =0.457, p=0.065) was found between CD-RISC score and frequency of prosthesis use for patients with a prosthesis (n=17).
CD-RISC scores in patients who did not report persistence of CRPS-I related symptoms (n=11) (median: 81, IQR: 76; 83) was higher compared to patients who did report these symptoms (n=15) (median: 71, IQR: 64; 78) (Mann Whitney U: p=0.032). CD-RISC scores were significantly lower in patients reporting more stump pain (ρ=-0.508, p=0.008). For phantom pain such an association was not found (ρ=-0.297, p=0.14). CD-RISC scores did not differ significantly between patients with or without objectified recurrence of CRPS-I (Mann Whitney U: p=0.53).

Table 3. Correlations between CD-RISC and WHOQOL-Bref scores and between CD-RISC and SCL-90-R in patients with amputation because of longstanding therapy-resistant CRPS-I.

	Correlation coefficient	***p***
WHOQOL-Bref [21]	0.549	0.004
Physical	0.454	0.020
Psychosocial	0.721	<0.001
Social	0.448	0.022
Environmental	0.407	0.039
SCL-90-R[22]		
Anxiety	−0.586	0.002
Agoraphobia	−0.405	0.040
Depression	−0.680	<0.001
Somatization	−0.439	0.025
Insufficiency	−0.543	0.004
Sensitivity	−0.539	0.005
Hostility	−0.660	<0.001
Insomnia	−0.391	0.048
Psychoneuroticism	−0.668	<0.001

WHOQOL-Bref: World Health Organization Quality of Life-BREF questionnaire. Resilience was measured with Connor-Davidson Resilience Scale (CD-RISC). Correlation Coefficient: between CD-RISC and SCL-90-R or CD-RISC and WHOQOL-Bref scores, calculated with Spearman's Rho

Discussion

This research focused on resilience (the ability to bounce back from adversity) in a group of patients with an amputation because of longstanding therapy-resistant CRPS-I. Resilience is an interactive concept concerning the combination of serious risk experiences and a relatively positive psychological outcome despite those experiences.[26] Higher resilience is positively related to better physical functioning, higher quality of life and lower pain scores among patients with chronic

conditions.[27-29] In a previous publication we showed relatively high quality of life scores in this group of patients with amputation due to longstanding therapy-resistant CRPS-I.[6] Based on the findings in literature and our own study [6],we hypothesized that patients with a CRPS-I related amputation who have relatively good results also score relatively high on resilience. We found a positive association between resilience and quality of life, especially within the psychosocial domain. Despite living with CRPS-I for many years and experiencing an amputation, scores on the psychosocial domain are significantly better than patients with chronic pain who visit the psychologist at a rehabilitation outpatient clinic and similar to Dutch norm values [20]. Even on the physical domain they score significantly better than the chronic pain patients.

The focus of most previous research on CRPS-I has been on risk factors. With an unknown cause of the CRPS-I, it is frequently assumed that psychological factors play an important role in the development of the syndrome. However, a systematic review showed that life events appear to be the only factor related to the development of CRPS-I; patients who experience more life events have a higher chance of developing CRPS-I.[30] Amputation because of CRPS-I is controversial due to clinicians' opinions on the negative outcome. Literature on amputation because of CRPS-I also focuses on reasons (risk factors) for amputation.[8] Case studies on amputation due to longstanding therapy-resistant CRPS-I are characterized by predominantly negative reporting on topics such as pain, quality of life, mobility and use of a prosthesis.[8] Recurrence of the syndrome underlies most opinions about not to amputate in case of longstanding therapy-resistant CRPS-I. However recurrence is often not (clearly) described in those case reports.[8] Our clinical experience with these patients led us to believe in a more positive outcome after amputation regarding quality of life.[6] Shifting the focus of research from identification of risk factors to this more positive approach on patients' competencies and strengths, offers a new perspective.

We are aware of the limitations of this study. Clinical relevance of differences in CD-RISC scores is not yet clear. A 7 point difference between our group and a non-help seeking population on a 0-100 scale (in which the upper and lower boundaries are never occur) seems to be meaningful (Table 1). Another limitation is that we do not have pre- and post-test measurements. This is also applicable for the results of the control group with chronic pain. Patients from this control group seek medical care for their (pain) problem, which is not necessarily the case for the CRPS-I and amputation population. Measurements presented from this control group are scores at the beginning or during the rehabilitation process and not after the rehabilitation process which makes comparing the results difficult. We do believe that this control group is more or less comparable to our CRPS-I population since both groups have been dealing with pain for a longer period.

Several explanations for relatively high resilience scores can be thought of. First, the high resilience scores in our study may be related to patient selection. It is possible that the specialists who made the decision to amputate unknowingly selected patients on the basis of resilience; the patient's previous ability to bounce back from adversity. According to this explanation our patients were more likely to have better outcome than could be expected based on literature. Whether this phenomenon

occurred is unclear since we have no information about the patients who were denied amputation. It may also be that only the most resilient patients with CRPS-I do not give up on looking for a solution in the face of repeated treatment failures. Another explanation for relatively high scores on questionnaires in general for this specific population years after amputation could be a phenomenon called response shift. Response shift means that, over time, the meaning of self-reported constructs are subject to change because of recalibration, reprioritization and reconceptualization [31,32].

Another factor that should be considered in explaining our results is the cognition of the patients. It is not unreasonable to assume that patients respond positively to their "last resort"; an amputation of their limb affected by longstanding therapy-resistant CRPS-I. Additionally patients may feel understood or feel that their problems are being taken seriously when, *at last* a team of medical specialists is found willing to deliberate amputation. Although the mechanism is poorly understood, the positive effect of clinician-patient communication on outcomes has been found repeatedly in other pathologies.[33]

Another explanation of the score may lie in the intervening period between amputation and our study. Life experiences between these two points may also have given a raise in resilience scores and accounts for one of the limitations of this study. Finally, cognitive dissonance could explain the relatively good results. Cognitive dissonance is the discomfort caused by holding conflicting cognitions. Based on that theory, the patient will try to minimize regret of their irrevocable choice.[34] These three explanations should be taken into account in future research in this field.

The domain scores of the SCL-90-R correlated negatively with resilience. These findings indicate that participants with a better resilience experience less psychological distress which is in line with our hypothesis. This negative correlation between resilience and psychological distress was found previously in women with fertility problems.[35] Not all associations were in line with our hypothesis. We expected that patients with a higher resilience score would improve in a larger number of topics. However, the association between resilience and the amount of topics patients improved upon was weak and not significant. Another "logical" hypothesis would be that those patients with a higher resilience score would use their prosthesis more often. The association between resilience and frequency of prosthesis use was not significant either ($p=0.065$). This lack of significance could be attributed to lack of power due to the small sample size. However, it is very well possible that resilient patients find ways of participating without the use of a prosthesis.

The direction of the association between resilience and quality of life remains unclear because of the study design. It is possible that the relatively good results encourage the patients to feel resilient rather than resilience leading to better results and the competency to restore parts of life. Programs for improving resilience are currently being developed and studied for effectiveness. The results of these programs substantiate that training can improve resilience.[36] Resiliency training may indirectly lead to improvement in quality of life.[37, 38] When patients ask for an amputation for their therapy-resistant CRPS-I a training to improve resilience prior to the amputation might be considered.

Medical care is known to influence a patient's quality of life, therefore rehabilitation after amputation plays an important role in the final results. Rehabilitation in our patient group, however, took place near patients' homes in different centres for rehabilitation in all parts of the country. Therefore, we cannot estimate the effect of it on the outcome.
Despite our relatively positive results, amputation for CRPS-I remains controversial. Screening for psychopathology and assessment of resilience should be performed prior to amputation.
We think that resilience might be a key factor in helping patients to accept and adapt to their new situation. Longitudinal studies are needed to analyze the strength of resilience over time and to analyze its prognostic value. Exploring competencies offers a new perspective on why some patients report positive outcomes after amputation. We conclude that the results of this explorative study confirm our hypotheses.

References

1. Stanton-Hicks M, Janig W, Hassenbusch S, Haddox JD, Boas R, Wilson P. Reflex sympathetic dystrophy: Changing concepts and taxonomy. Pain 1995 10;63(0304-3959; 1):127-33.
2. Perez RS, Zollinger PE, Dijkstra PU, Thomassen-Hilgersom IL, Zuurmond WW, Rosenbrand CJ, Geertzen JH. [Clinical practice guideline 'complex regional pain syndrome type I']. Ned Tijdschr Geneeskd 2007 07/28;151(0028-2162; 0028-2162; 30):1674-9.
3. de Mos M, Huygen FJ, van der Hoeven-Borgman M, Dieleman JP, Ch Stricker BH, Sturkenboom MC. Outcome of the complex regional pain syndrome. Clin J Pain 2009 09;25(1536-5409; 7):590-7.
4. Geertzen JH, Rietman JS, Smit AJ, Zimmerman KW. A young female patient with reflex sympathetic dystrophy of the upper limb in whom amputation became inevitable. Prosthet Orthot Int 1997 08;21(0309-3646; 2):159-61.
5. Dielissen PW, Claassen AT, Veldman PH, Goris RJ. Amputation for reflex sympathetic dystrophy. J Bone Joint Surg Br 1995 03;77(0301-620; 2):270-3.
6. Krans-Schreuder H, Bodde M, Schrier E, Dijkstra P, Van den Dungen J, Den Dunnen W, Geertzen J. Amputation in longstanding, therapy-resistant CRPS-I. J Bone Joint Surg Am. 2012 Dec 19;94(24):2263-8.
7. Hohendorff B, Muhldorfer-Fodor M, van Schoonhoven J, Prommersberger KJ. Amputation of the hand as last resort in severe complex regional pain syndrome. Handchir Mikrochir Plast Chir 2011 Oct;43(5):307-12.
8. Bodde MI, Dijkstra PU, den Dunnen WF, Geertzen JH. Therapy-resistant complex regional pain syndrome type I: To amputate or not? J Bone Joint Surg Am 2011 Oct 5;93(19):1799-805.
9. Emmelot CH, Spauwen PH, Hol W, Overbeek B. Trans-tibial amputation for reflex sympathetic dystrophy: Postoperative management. Prosthet Orthot Int 2000 04;24(0309-3646; 1):79-82.

10. Lundborg C, Dahm P, Nitescu P, Appelgren L, Curelaru I. Clinical experience using intrathecal (IT) bupivacaine infusion in three patients with complex regional pain syndrome type I (CRPS-I). Acta Anaesthesiol Scand 1999 07;43:667-78.
11. Stam HJ, Van der Rijst H. The results of amputation in reflex sympathetic dystrophy of the upper extremity - an analysis of 7 cases. Eur J Phys Med Rehabil 1994;4(4):134-6.
12. Perez RS, Zollinger PE, Dijkstra PU, Thomassen-Hilgersom IL, Zuurmond WW, Rosenbrand KC, Geertzen JH, CRPS I task force. Evidence based guidelines for complex regional pain syndrome type 1. BMC Neurol 2010 Mar 31;10:20,2377-10-20.
13. Goebel A, Barker C.H., Turner-Stokes L., et al. Complex regional pain syndrome in adults: UK guidelines for diagnosis, referral and management in primary and secondary care. London: RCP; 2012.
14. Stewart DE, Yuen T. A systematic review of resilience in the physically ill. Psychosomatics 2011 May-Jun;52(3):199-209.
15. The Road to Resilience [Internet] [cited 2013 . Available from: http://www.lpac.ca/main/PDF/Road%20to%20Resilience.pdf.
16. Connor KM, Davidson JR. Development of a new resilience scale: The connor-davidson resilience scale (CD-RISC). Depress Anxiety 2003;18(2):76-82.
17. Ferguson AD, Richie BS, Gomez MJ. Psychological factors after traumatic amputation in landmine survivors: The bridge between physical healing and full recovery. Disabil Rehabil 2004 Jul 22-Aug 5;26(14-15):931-8.
18. Merskey H, Bogduk N. Classification of chronic pain: descriptions of chronic pain syndromes and definitions of pain terms. Seattle: IASP Press; 1994:40–3.
19. Bruehl S, Harden RN, Galer BS, Saltz S, Bertram M, Backonja M, Gayles R, Rudin N, Bhugra MK, Stanton-Hicks M. External validation of IASP diagnostic criteria for complex regional pain syndrome and proposed research diagnostic criteria. international association for the study of pain. Pain 1999 05;81:147-54.
20. Giesbrecht T, Abidi K, Smeets T, Merckelbach H, Van Oorsouw K, Raymaekers L. Adversity does not always lead to psychopathology: Cognitive reactivity is related to longitudinal changes in resilience. Netherlands J Psychology 2009;65:62-8.
21. Skevington SM, Lotfy M, O'Connell KA, WHOQOL Group. The World Health Organization's WHOQOL-BREF quality of life assessment: Psychometric properties and results of the international field trial. A report from the WHOQOL group. Qual Life Res 2004 Mar;13(2):299-310.
22. Arrindell WA, Ettema JHM. Symptom checklist. handleiding bij een multidimensionele psychopathologie-indicator. Lisse: Swets Test Publishers; 2003.
23. Masthoff ED, Trompenaars FJ, Van Heck GL, Hodiamont PP, De Vries J. Quality of life and psychopathology: Investigations into their relationship. Aust N Z J Psychiatry 2006 Apr;40(4):333-40.
24. Altman DG, Machin D, Bryant TN, Gardner MJ. Statistics with confidence 2nd edition.London: BMJ Books; 2000.
25 . Ek JW, van Gijn JC, Samwel H, et al. Pain exposure physical therapy may be a safe and effective treatment for longstanding complex regional pain syndrome type 1: a case series. Clin Rehabil 2009;23:1059–66.

26. Rutter M. Implications of resilience concepts for scientific understanding. Ann N Y Acad Sci 2006 Dec;1094:1-12.
27. Chan I, Lai J, Wong K. Resilience is associated with better recovery in chinese people diagnosed with coronary heart disease. Psychol Health 2006 06;21(3):335-49.
28. Wright LJ, Zautra AJ, Going S. Adaptation to early knee osteoarthritis: The role of risk, resilience, and disease severity on pain and physical functioning. Ann Behav Med 2008 Aug;36(1):70-80.
29. Farber EW, Schwartz JA, Schaper PE, Moonen DJ, McDaniel JS. Resilience factors associated with adaptation to HIV disease. Psychosomatics 2000 Mar-Apr;41(2):140-6.
30. Beerthuizen A, van 't Spijker A, Huygen FJ, Klein J, de Wit R. Is there an association between psychological factors and the complex regional pain syndrome type 1 (CRPS1) in adults? A systematic review. Pain 2009 Sep;145(1-2):52-9.
31. Streiner DL, Norman GR. Health measurement scales; a practical guide to their development and use. fourth ed. Oxford, University press; 2008.
32. Schwartz CE, Sprangers MA. Methodological approaches for assessing response shift in longitudinal health-related quality-of-life research. Soc Sci Med 1999 Jun;48(11):1531-48.
33. Street RLJ, Makoul G, Arora NK, Epstein RM. How does communication heal? pathways linking clinician-patient communication to health outcomes. Patient Educ Couns 2009;74 (3):295-301.
34. Homer JJ, Sheard CE, Jones NS. Cognitive dissonance, the placebo effect and the evaluation of surgical results. Clin Otolaryngol Allied Sci 2000 Jun;25(3):195-9.
35. Sexton MB, Byrd MR, von Kluge S. Measuring resilience in women experiencing infertility using the CD-RISC: Examining infertility-related stress, general distress, and coping styles. J Psychiatr Res 2010 Mar;44(4):236-41.
36. Vetter S, Dulaev I, Mueller M, Henley RR, Gallo WT, Kanukova Z. Impact of resilience enhancing programs on youth surviving the beslan school siege. Child Adolesc Psychiatry Ment Health 2010 Apr 22;4:11.
37. Loprinzi CE, Prasad K, Schroeder DR, Sood A. Stress management and resilience training (SMART) program to decrease stress and enhance resilience among breast cancer survivors: A pilot randomized clinical trial. Clin Breast Cancer. 2011 Dec;11(6):364-8
38. Sood A, Prasad K, Schroeder D, Varkey P. Stress management and resilience training among department of medicine faculty: A pilot randomized clinical trial. J Gen Intern Med 2011 Aug;26(8):858-61.

Chapter 6

Psychosocial factors associated with poor outcomes after amputation for complex regional pain syndrome type-I

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PLoS One. 2019 Mar 13;14(3):e0213589. doi: 10.1371

Abstract

Background
Amputation for longstanding therapy resistant complex regional pain syndrome type-I (CRPS-I) is controversial. Reported results are inconsistent. It is assumed that psychological factors play a role in CRPS-I.
Objective
To explore which psychological factors prior to amputation are associated with poor outcomes after amputation in the case of longstanding therapy resistant CRPS-I.
Methods
Between May 2008 and August 2015, 31 patients with longstanding therapy resistant CRPS-I were amputated. Before the amputation 11 psychological factors were assessed. In 2016, participants had a structured interview by telephone and filled out questionnaires to assess their outcome. In case of a perceived recurrence of CRPS-I a physician visited the patient to examine the symptoms. Associations between psychological factors and poor outcomes were analysed.
Results
Four of the 11 psychological factors were associated with poor outcomes. Regression analyses showed that change in the worst pain in the past week was associated with poor social support (B=0.3, 95% confidence interval: 0.1;0.6) and intensity of pain before amputation (B=2.0, 95% confidence interval 0.9;3.0). Patients who reported important improvements in mobility (n=23) had significantly higher baseline resilience (median 79) compared to those (n=8) who did not report it (median 69)(Mann-Whitney U, Z=-2.398, p=0.015). Being involved in a lawsuit prior to amputation was associated with a recurrence in the residual limb (Bruehl criteria). A psychiatric history was associated with recurrence somewhere else (Bruehl criteria).
Conclusion
Poor outcomes of amputation in longstanding therapy resistant CPRS-1 are associated with psychological factors. Outstanding life events are not associated with poor outcome although half of the participants had experienced outstanding life events.

Introduction

Complex regional pain syndrome type-I (CRPS-I) is characterized by severe pain, sensory, vasomotor, sudomotor and trophic changes and can have a devastating effect on a person.[1] CRPS-I generally develops after an injury but sometimes it develops spontaneously. Many treatments have been described but only a few are evidence based.[2] Amputation in the case of longstanding therapy resistant CRPS-I is rare and controversial. It is rare because many patients with CRPS-I, recover within 6 to 13 months.[3] It is controversial because some patients benefit from the amputation, while others experience the same symptoms or even experience an increase of symptoms after the amputation.[4] These unpredictable outcomes make an amputation in longstanding therapy resistant CRPS-I debatable as treatment.[5] Hesitation to amputate is strengthened by the assumed role of psychological factors or psychiatric disorders in the aetiology, development and maintenance of CPRS-

I.[6-10] However, data supporting this assumption are scant. In the University Medical Centre Groningen (UMCG) the decision to amputate or not is made by a team of specialists together with the patient.[11] For the psychologist, working in that team, a working hypothesis was that outcomes of an amputation would be negatively influenced by presence of some psychological factors: Poor Quality of Life (QOL) in the physical domain or psychological domain, low resilience, depression, anxiety, psychological distress, childhood adversity, life events, psychiatric (DSM-IV) history or psychiatric disorder, current lawsuit, and or poor social support.[12-14] In patients with an amputation for other causes, associations with poor QOL post amputation have been reported.[15-17] Poor QOL was associated with many factors including depression, social support, cognition, pain, independence in activities of daily living and comorbidity.[18, 19] Starting in May 2008 these factors were therefore routinely assessed during intake of patients who requested an amputation in the case of longstanding therapy resistant CRPS-I in our centre. Insight regarding which psychological factors are associated with poor outcomes could help the team to predict which patients suffering from longstanding therapy resistant CRPS-I should not be amputated. Current study is part of a larger outcome study of CRPS-I patients, amputated in the UMCG, starting in 2000. Of all the 48 patients participating in that study, 31 were assessed by a psychologist (ES) prior to amputation by means of a standardized interview and a set of questionnaires. The larger study focuses on several outcomes after amputation, assessed in 2015, but is cross-sectional in design. Focus of current study was to explore which psychological factors assessed prior to amputation are associated with poor outcomes after amputation.

As primary outcomes of this study change in pain and mobility after amputation were selected because most patients requested an amputation to improve on pain and or mobility. As a secondary outcome recurrence of CRPS-I was selected because after amputation recurrence in the residual limb or elsewhere is a major concern.[4, 5] The aim of this longitudinal study was to analyse changes over time and to explore which psychological factors, present prior to amputation, were associated with poor outcomes after amputation in the case of longstanding therapy resistant CRPS-I.

Methods

The research protocol was approved by the local Medical Research Ethics Committee (METc 2015/561) and all participants signed an informed consent before the start of the study.

Between May 2008 and August 2015, 33 adult patients with longstanding, therapy resistant CRPS-I underwent an amputation at the UMCG. CRPS-I was determined to be therapy resistant if all treatments described in the Dutch guidelines for CRPS-I had been tried.[20] Inclusion criteria for this follow-up study were: 18 years or older, participants should be able to comprehend questionnaires, and amputation was performed at least 1 year prior to follow-up. All 33 patients were asked to participate and all met inclusion criteria for this study. One patient did not respond and 1 patient had passed away. All participants met Bruehl criteria for CRPS-I at the time of amputation.[1]

More patients with longstanding therapy resistant CRPS-I requested an amputation at our Centre, but in about 50% of patients the requested amputation was refused. The main reasons to refuse were: criteria for CRPS-I were not met, patient expectations about the effects of an amputation were too optimistic (not realistic), the onset of CRPS-I was less than 1 year ago or all treatments described in the Dutch guidelines for CRPS-I had not yet been tried.[20]
Between May 2008 to August 2015, during the psychological assessment for the decision making process to amputate or not, a structured interview with the patient was performed. In that interview pain, childhood adversity, outstanding life events, a current lawsuit, a psychiatric disorder or history of a psychiatric disorder were assessed. Childhood adversity was operationalized as any experience(s), such as physical, mental or sexual abuse, occurring in childhood that cause(s) extreme stress. An outstanding life event was operationalized as any experience that caused stress far above the average. Additionally, a set of questionnaires was filled out.
In April 2016 an invitational letter to participate in this follow-up study was send to 33 patients. The follow-up study included a structured interview by telephone and filling out of questionnaires. Between May 30 2016 and August 11 2016 the structured interviews were held by a physician (JS), not involved in the decision making process of the amputation. Participants were also send a link to a secure website with the request to fill out a set of questionnaires. Attempts to acquire data were stopped January 1 2017.
In the interview, participants were asked to rate their worst and their least pain, in the past week, on a numeric rating scale (NRS): 0 = no pain and 10 = the worst imaginable pain. Participants were asked to rate their change in mobility after amputation, compared to the mobility prior to amputation, on a 5 point Likert scale (important improvement, small improvement, no change, small deterioration or important deterioration). If the participant reported a recurrence of CRPS-I, the physician (JS) visited the patient to evaluate recurrence according to Bruehl criteria.[20]
The following questionnaires were filled out prior to amputation and at follow-up.
The Quality of Life Questionnaire (WHOQOL-BREF) was used to assess quality of life in 4 different domains. It is a 26 item questionnaire that correlates well with the original 100 item questionnaire (r ranges from 0.88 to 0.96).[21] The WHOQOL-BREF has been field-tested widely.[22] In this study we used 3 domains of the questionnaire; physical health (7 items), psychological health (6 items) and social relationships (3 items). Raw data were transformed into domain scores range from 4 to 20 following the guidelines.[23] A higher score indicates a better QOL. The social relationships scale was used to determine social support. One question of this scale assesses satisfaction with support of friends and 1 assesses satisfaction with personal relationships. We operationalized poor social support as a score 1SD below the mean of all participants.
The Connor-Davidson Resilience Scale (CD-RISC), a 25 item questionnaire, was used to evaluate resilience. Each item is rated on a 5-point scale. The score ranges from 0 to 100, with higher scores reflecting greater resilience. Resilience can be viewed as a measure of stress coping ability.[24]

The hospital anxiety and depression scale (HADS) was used to assess anxiety and depression.[25] This scale is divided into 2 subscales, an anxiety subscale (HADS-A) and a depression subscale (HADS-D), both containing 7 items. Each item is rated on a 5-point scale. The Cronbach alpha was .83 for the anxiety subscale and .84 for the depression subscale, indicating adequate internal consistency.[26] The HADS was added to the standard intake procedure in 2009 hence five participants did not fill out the HADS at T0.
The Symptom Check List-90-Revised (SCL-90-R) assesses self-reported psychological distress and multiple aspects of psychopathology. It consists of 90 questions, each item is rated on a 5-point scale. In this study total scale was used as a measure for psychological distress.[27] Internal consistency of the total scale is excellent.[28] The SCL-90-R was added to the standard intake procedure in 2010, hence 9 participants did not fill out the SCL-90-R at T0.

Statistical procedures

Data was anonymised. Changes in pain scores (intensity of worst and least pain of the past week), domain scores of the WHOQOL-BREF (physical, psychological, and social), resilience scores, and HADS scores (depression and anxiety) were checked for normal distribution. Changes were normally distributed, hence a paired-sample t-test was applied.
We operationalized the outcome variables as follows. A poor outcome regarding pain (the worst pain in the past week) was present if the improvement was <2 points on the NRS.[29] A poor outcome regarding mobility was present if the participant rated the change as less than an "important" improvement. A poor outcome regarding CRPS-I was present if the physician judged CRPS-I to be present (in the residual limb or elsewhere), based on Bruehl criteria. [1]
The following potential risk factors, assessed prior to amputation, were explored, for their association with poor outcomes; low scores on the physical, psychological, or social domains of the WHOQOL-BREF (a score of 1 SD below the mean of all participants), poor resilience, (a score of 1 SD below the mean of all participants), a score >8 on one of the HADS domains, psychological distress (a score of 1 SD above the mean of all participants on the SCL-90-R), childhood adversity, outstanding life events, a psychiatric disorder or history of a disorder, and being involved a lawsuit. Uni variable linear regression analyses were performed for all 11 potential risk factors and 5 baseline characteristics (social status, age, gender, education and pain) as independent variables, with change in worst pain in the past week (before and after amputation) as dependent variable. Dummy variables were made to analyse social status, level of amputation and education. Factors associated ($p<0.1$) with change in worst pain in the past week, were entered in multi variable regression analysis. The following factors, assessed prior to amputation, were entered: worst pain intensity in the past week, social support and education. All 11 potential risk factors and 5 baseline characteristics, were also analysed non-parametrically for their association with poor outcomes regarding mobility and recurrence. Associations with mobility were analysed using a Mann-Whitney test and associations with recurrence were analysed using Fischer's exact test. Results are significant at $p\leq0.05$ unless stated otherwise. All analyses were performed in IBM SPSS Statistics (v.22).

Results

Thirty-one patients, mean (sd) age 41 (12.1), 6 men and 25 women, participated (Table 1).

Table 1 Clinical characteristics of 31 participants.

Variable	Mean(SD) T0	n(%) T0
Age (years)	37.5(12.5)	
Women		25(81)
Social status		
Living alone		8(26)
Living together		16(52)
Living with parent(s)		7(22)
Education (ISCES level)		
0-4		9(29)
5 and 6		18(58)
7-9		4(13)
Presence of		
Childhood adversity		10(32)
Outstanding life events		16(52)
Lawsuit		2(6)
Psychiatric disorder or history of such a disorder		6(19)
Motivation for amputation request±		
Pain reduction		31(100
Contracture		23(74)
Increase mobility		19(61)
Remove "obstacle"		12(39)
Non-functional limb		8(26)
Wounds		8(26)
Dystonia		3(10)
Duration CRPS-I prior to amputation (years)		7.4(6.9)
	Mean(SD) T1	**n(%) T1**
Age (years)	41.4(12.1)	
Level of amputation		
Trans-humeral		1(3)
Trans-radial		1(3)
Trans-femoral		6(19)
Knee disarticulation		10(32)
Trans-tibial		13(42)
Time after amputation(years)	3.9(2.2)	

T0= Prior to amputation, T1= Follow-up, ISCES= The International Standard Classification of Education
±=More answers possible

Table 2 Scores before and after amputation and difference in mean scores in 31 patients.

				95% confidence interval of difference		
Variable	**Mean (SD) T0**	**Mean (SD) T1**	**Differen-ce (SD)**	**Lo-wer**	**Up-per**	**P***
Intensity of worst pain in past week	8.7(0.9)	5.2(3.0)	-3.5 (3.3)	-2.2	-4.7	<.001
Intensity of least pain in past week	6.1(1.8)	2.5(2.9)	-3.6 (3.3)	-2.4	-4.8	<.001
Quality of life Physical domain	9.4(2.5)	12.7(3.7)	3.3 (3.6)	4.6	2.0	<.001
Quality of life Psychological domain	14.1(2.1)	14.6(3.3)	0.5 (2.5)	1.4	0.5	.329
Quality of life Social domain	13.6(3.8)	14.3(3.0)	0.8 (3.5)	2.1	0.5	.230
Resilience CD-RISC	76.9(9.2)	72.5(17.8)	-4.5 (13.7)	-0.6	-9.5	.081
HADS depression (n=26)#	5.2 (3.4)	3.4 (4.5)	-1.8 (4.6)	-0.1	-3.6	.063
HADS anxiety (n=26)#	5.1 (3.1)	4.0 (3.6)	-1.0 (3.3)	-0.3	-2.4	.127
SCL-90-R(n=22)#	128.7(26.2)	148.7(55.7)	20 (44.9)	39.9	0.1	.049

T0= Prior to amputation, T1= Follow-up, *=Significance results of paired-sample t test, # =Number of paired data if less than 31.
Scale range: pain; 0-10, Quality of life domains; 0-20, Resilience 0-100, HADS domains 0-21, SLC-90; 90-360

At follow up pain scores had reduced, scores on the physical domain of the QOL were improved, and SCL-90-R scores had increased ($p<0.05$)(Table 2).
An overview of potential risk factors and outcomes per patient is presented in Table 3.

Table 3 Potential risk factors and outcomes of an amputation in longstanding therapy resistant CRPS-I.

Partici-pant	Risk factors				Outcomes			
	Resilience score	Social support	Law-suit	Psychiatric disorder DSM4	Pain change	Mobility change	Recurrence, residual limb	Recurrence, somewhere else
1	76	12	N	N	9	++	N	N
2	66	12	N	N	9	++	N	N
3	67	17	N	N	9	+	N	N
4	77	11	N	N	8	++	N	N
5	82	17	N	N	7	++	N	N
6	69	20	N	N	7	+	N	N
7	71	17	N	Y	7	++	N	N
8	91	17	N	N	7	++	N	N
9	71	16	N	N	6	++	N	N
10	69	15	N	Y	6	+	N	N
11	90	11	N	N	5	++	N	N
12	85	17	N	N	4	++	N	N
13	80	13	Y	N	4	+	Y	N
14	88	16	N	N	4	++	N	N
15	76	15	N	N	3	++	N	N
16	70	9	N	N	3	++	N	N
17	88	20	N	N	3	++	N	N
18	87	8	N	N	2	++	N	N
19	66	12	N	N	2	++	Y	Y
20	69	12	N	HIS	2	+	N	N
21	81	11	Y	N	1	+-	Y	Y
22	76	12	N	Y	1	++	N	N
23	64	12	N	N	1	++	N	N
24	59	9	N	N	1	+	N	N
25	69	11	N	HIS	1	--	N	N
26	83	19	N	N	0	++	Y	N
27	95	19	N	N	0	++	N	N
28	83	11	N	N	0	++	Y	N
29	79	5	N	N	-1	++	N	N
30	71	9	N	N	-2	++	N	N
31	86	15	N	HIS	-2	++	N	N

Resilience score = total score of CD-RISC, Social support = total score of social domain at initial assessment, Y = Potential predictor is present prior to amputation, N=not present HIS=history of psychiatric disorder prior to amputation, Pain change= change in worst pain in past week, higher values indicate larger improvements, Mobility change = mobility change between before and after amputation; ++= Important improvement, += small improvement, +-= no change, ---= important deterioration, Recurrence according to Bruehl criteria: Y = outcome is present at follow up, N=not present ;GRAY SHADED Risc factors= potential predictor of poor outcome; GRAY SHADED Outcomes= outcome is poor (see text for operationalisations).

Eleven participants (35%, 95% confidence interval (CI) 21% to 53%) had a poor outcome regarding pain, 8 participants (26%, 95% CI 14% to 43%) had a poor outcome regarding mobility and 12 participants (39%,95%CI 24% to 56%) reported a recurrence. Of these 12 participants 5 (16%, 95% CI 7% to 33%) had a recurrence confirmed by a physician following Bruehl criteria. Seven patients (23%, 95% CI 11% to 40%) had 2 poor outcomes and 1 participant (3%, 95% CI 1% to 16%) had 3 poor outcomes. Reduction of worst pain in the last week was less in participants with a poor social support (Table 4).

Table 4 Results of the 2 regression analyses with change in worst pain in the past week as dependent variable. Model 1 without controlling for education, model 2 with controlling for education.

Model		Unstandardized Coefficients			95% Confidence Interval for B		Model correlation	
		B	SE B	Sig.	Lower Bound	Upper Bound	R	R Square change
1	(Constant)	-20.8	5.1	<0.001	-31.1	-10.4	0.679	.461 p<0.001
	Social support	0.4	0.1	0.004	0.1	0.6		
	Pain[a]	2.2	0.5	<0.001	1.1	3.2		
2	(Constant)	-18.8	4.9	0.001	-28.8	-8.7	0.741	.088 p=0.099
	Social support	0.3	0.1	0.011	0.1	0.6		
	Pain[a]	2.0	0.5	0.001	0.9	3.0		
	Education high[b]	3.3	1.5	0.037	0.2	6.4		
	Education middle [b]	0.6	1.0	0.563	-1.5	2.6		

a: Worst pain in the past week assessed prior to amputation b: the reference group for education low education.

Participants with low resilience perceived a less important improvement in mobility score (Mann-Whitney U, Z= -2.398, p= 0.015, median resilience of those with an important improvement n=23: 79 and median resilience of others n=8: 69). No other variables were associated with an important improvement in mobility. Twelve participants (38%, 95%CI 24% to 56%) believed they had recurrence of the CRPS-I in the residual limb and 8 (26%, 95%CI 14% to 43%) believed somewhere else. According to Bruehl criteria, 5 participants (16%, 95%CI 7% to 33%) had a recurrence in the residual limb and 2 participants (6%, 95%CI 2% to 21%) also somewhere else.
Being involved in a lawsuit was associated with a recurrence in the residual limb (Bruehl criteria). A psychiatric disorder or history of psychiatric disorder was associated with a recurrence somewhere else (Bruehl criteria) and with reporting a recurrence somewhere else (Table 5).

Table 5. Associations of psychological factors and poor outcome of an amputation in longstanding therapy resistant CRPS-I in 31 patients.

	Recurrence	**No recurrence**	**significance**
	In residual limb (Bruehl, n=5)	In residual limb (Bruehl, n=26)	
Psychiatric[a] (n=6)	2	4	0.241
Lawsuit[b] (n=2)	2	0	0.022*
	Somewhere else (Bruehl, n=2)	Somewhere else (Bruehl, n=29)	
Psychiatric[a] (n=6)	2	4	0.032*
Lawsuit[b] (n=2)	1	1	0.127
	Patient reported in residual limb (n=12)	Patient reported in residual limb (n=19)	
Psychiatric[a] (n=6)	4	2	0.137
Lawsuit[b] (n=2)	2	0	0.142
	Patient reported somewhere else (n=8)	Patient reported somewhere else (n=23)	
Psychiatric[a] (n=6)	4	2	0.026*
Lawsuit[b] (n=2)	2	0	0.060

a) Psychiatric disorder or history of psychiatric disorder prior to amputation, b) Patient was in a lawsuit prior to amputation, *= <0.05 Results of Fischer exact test.

No other associations were found between potential risk factors and outcome variables.

Discussion

This study focussed on associations between psychological factors before amputation and poor outcomes after amputation because of longstanding therapy resistant CRPS-I. Four risk factors were associated with poor outcomes. Poor social support or lower score on resilience were associated with poor outcomes regarding pain and mobility. Having a psychiatric disorder or a history of a psychiatric disorder or involvement in a lawsuit were associated with recurrence.
Amputation in longstanding therapy resistant CRPS-I is a last option but outcomes can be disappointing. Therefore identifying risk factors associated with poor outcome is highly relevant. The association between lack of social support and pain was more or less expected since lack of social support is also a predictor of worse outcomes in patients with arthritis, chronic pain, and patients with an amputation.[30-33] The fact that social support is beneficial for many patients points in the direction of a more general principal and not specific for CRPS-I. We did not find an association between change in worst pain in the past week and anxiety before the amputation (HADS-A). A prospective study into psychological factors, influencing recovery from

CRPS-I found an association between high anxiety scores and poor outcome.[34] The main difference with our study is, that in our study participants suffered from longstanding therapy resistant CRPS-I, while in the mentioned study patients responded to treatment of their CRPS-I. Additionally we used different questionnaires to asses anxiety. Contrary to our assumption no association was found between poor outcomes and childhood adversity or outstanding life events. About one third of the participants, had experienced childhood adversity, and more than half had experienced outstanding life events (including childhood adversity). A high incidence of life events in CRPS-I patients was also found in other studies.[35, 36] Childhood adversity or outstanding life events were found to be factors predisposing for chronic pain.[13, 36, 37] The way people handle stress can be weakened by (prolonged) adversity especially in childhood.[38] However, a subgroup of people benefit from a stressful environment and learn to cope better with stress.[39, 40] In our study most participants had normal to high stress coping ability or resilience. It is possible that participants with childhood adversity and outstanding life events in our study, coped well with adversity. But it is still thinkable that stressful periods might contribute to development of CRPS-I, although we did not find any association between presence of stressful life events and recurrence. Participants with low resilience less often perceived an important improvement in their mobility. Such an association was expected, because resilience is a factor that can influence outcome in physically ill people.[41, 42] One rationale is that disease is a stressful event and the way somebody copes with the stress (resilience or stress coping ability) is influencing the impact of the disease. In a previous cross sectional study in patients with an amputation because of longstanding therapy resistant CRPS-I we found that higher resilience scores were associated with a better QOL and lower psychological distress.[43] In that study we found that the resilience of our participants was above average. We wondered why. It might be that only the most resilient patients with CRPS-I are not giving up on looking for a solution after disappointing treatments and end up in a hospital for an amputation far from their home.

The expected association between depression and poor outcome was not found. This association was reported in studies in patients with CRPS-I and in patients after amputation.[15-17,34] But in a prospective multicenter cohort study an association between depression and development of CRPS-I was not found.[36]

In this study participants having a lawsuit before amputation had a higher chance of recurrence in the residual limb. Previous research reported, that being involved in a lawsuit may negatively impact on chronic pain.[44,45] We did not find a significant association. Although the medical examination confirmed recurrence of CRPS-I in the 2 patients that were in a lawsuit at the time of the intake, 1 participant reported a positive, but not clinical relevant, change in pain of 1 point while the other participant reported, a clinical relevant 4 points improvement after amputation and yet claiming recurrence. It is possible that experienced injustice plays a role in the way they experience their symptoms.

A psychiatric disorder or a history of a psychiatric disorder was associated with reported and observed recurrence somewhere else. Of the 6 participants with a psychiatric disorder or a history of a psychiatric disorder 4 didn’t have recurrence somewhere else. For that reason using a psychiatric disorder or a history of a

disorder as a potential risk factor for a poor outcome is not specific enough. Additionally a psychiatric disorder or a history of a psychiatric disorder is not precise since it could be any psychiatric disorder described in the DSM-IV and therefor it has limited value in the decision making process. The reason we analysed this potential risk factor, beside depression, anxiety and psychological distress, was the assumed role of a psychiatric disorder in the development of CRPS-I.[6-10] However several reviews could not confirm such a role.[36, 46] Prior to the amputation 3 participants (Table 3: participant 2, 7 and 16) had a potential risk factor for a poor outcome, but their mobility improved and pain decreased considerably, indicating that the prediction of outcomes, based on our findings, is currently not specific enough. A possible explanation is that also other factors, psychologically, physically and medically, play a role in outcomes after amputation because of longstanding therapy resistant CRPS-I. Other factors that also influence outcomes are the common therapeutic factors e.g. expectations or a placebo effect.[47, 48]
The risk factors identified in this study are also not sensitive. Four participants had no risk factors but had poor outcome in 1 or more outcomes (Table 3: participant 6, 26, 27 and 28). Table 3 illustrates the lack of clear pattern in associations. As already mentioned, possibly other factors or a cluster of factors not assessed in this study can predict outcomes better, such as pain related fear, catastrophic thinking, coping style or perception disturbance.[34] Patients ruminating about the worst case scenarios (catastrophic thinking) may interpret any bodily feeling as harmful. This mechanism may play a role in reporting of recurrence of CRPS-I (12 patients reported recurrence but CRPS-I was only confirmed in 5 cases by the physician). As a result of this study we added a scale for pain related fear and catastrophizing to our clinical practice. The data of this study do not support the assumed role of psychological factors or psychiatric disorders in the etiology, development and maintenance of CPRS-I. They do support the assumed role of psychological factors in rehabilitation.

Limitations of this study

A limitation of our study is the presence of ceiling effects of pain scores, 75% of the participants scored 9 or 10 on the NRC scale before amputation. Additionally the time between amputation and follow-up differed between participants (mean 3.9 years (SD2.2)). Other weaknesses are the use of 11 potential risk factors and 3 different outcomes in a small data set with some missing data of which only change in pain was normally distributed resulting in several non-parametric analyses. Some significant associations might be related to multiple testing.

Conclusion

Poor outcomes of amputation in longstanding therapy resistant CPRS-1 are associated with psychological factors.
These factors are not specific for the recovery or rehabilitation of CRPS-I.
Outstanding life events are not associated with poor outcomes although half the participants had experienced outstanding life events.

Conflict of interest

The authors declare that there is no conflict of interest.

Funding
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

References

1. Bruehl S, Harden RN, Galer BS, Saltz S, Bertram M, Backonja M, et al. External validation of IASP diagnostic criteria for Complex Regional Pain Syndrome and proposed research diagnostic criteria. International Association for the Study of Pain. Pain. 1999 May;81(1-2):147-54.
2. Bruehl S. Complex regional pain syndrome. BMJ. 2015 Jul 29;351:h2730.
3. Bean DJ, Johnson MH, Kydd RR. The outcome of complex regional pain syndrome type 1: a systematic review. J Pain. 2014 Jul;15(7):677-90.
4. Dielissen PW, Claassen AT, Veldman PH, Goris RJ. Amputation for reflex sympathetic dystrophy. J Bone Joint Surg Br. 1995 Mar;77(2):270-3.
5. Bodde MI, Dijkstra PU, den Dunnen WF, Geertzen JH. Therapy-resistant complex regional pain syndrome type I: to amputate or not? J Bone Joint Surg Am. 2011 Oct 5;93(19):1799-805.
6. Lohnberg JA, Altmaier EM. A review of psychosocial factors in complex regional pain syndrome. J Clin Psychol Med Settings. 2013 Jun;20(2):247-54.
7. Szeinberg-Arazi D, Heim M, Nadvorna H, Ner IZ, Szeinberg A, Azaria M. A functional and psychosocial assessment of patients with post-Sudeck atrophy amputation. Arch Phys Med Rehabil. 1993 Apr;74(4):416-8.
8. Bruehl S, Chung OY. Psychological and behavioral aspects of complex regional pain syndrome management. Clin J Pain. 2006 Jun;22(5):430-7.
9. de Asla RJ. Complex regional pain syndrome type I: disease or illness construction? Commentary on an article by Marlies I. Bodde, MD, et al.: "Therapy-resistant complex regional pain syndrome type I: to amputate or not?". J Bone Joint Surg Am. 2011 Oct 5;93(19):e116(1).
10. Turner-Stokes L. Reflex sympathetic dystrophy--a complex regional pain syndrome. Disabil Rehabil. 2002 Dec 15;24(18):939-47.
11. Bodde MI, Dijkstra PU, Schrier E, van den Dungen JJ, den Dunnen WF, Geertzen JH. Informed Decision-Making Regarding Amputation for Complex Regional Pain Syndrome Type I. J Bone Joint Surg Am. 2014 Jun 4;96(11):930-4.
12. Alschuler KN, Kratz AL, Ehde DM. Resilience and vulnerability in individuals with chronic pain and physical disability. Rehabil Psychol. 2016 Feb;61(1):7-18.
13. Burke NN, Finn DP, McGuire BE, Roche M. Psychological stress in early life as a predisposing factor for the development of chronic pain: Clinical and preclinical evidence and neurobiological mechanisms. J Neurosci Res. 2016 Jul 12.
14. Geertzen JH, Dijkstra PU, van Sonderen EL, Groothoff JW, ten Duis HJ, Eisma WH. Relationship between impairments, disability and handicap in reflex sympathetic dystrophy patients: a long-term follow-up study. Clin Rehabil. 1998;12(5):402-12.
15. Asano M, Rushton P, Miller WC, Deathe BA. Predictors of quality of life among individuals who have a lower limb amputation. Prosthet Orthot Int. 2008 Jun;32(2):231-43.

16. Horgan O, MacLachlan M. Psychosocial adjustment to lower-limb amputation: a review. Disabil Rehabil. 2004 Jul 22-Aug 5;26(14-15):837-50.
17. Zidarov D, Swaine B, Gauthier-Gagnon C. Quality of life of persons with lower-limb amputation during rehabilitation and at 3-month follow-up. Arch Phys Med Rehabil. 2009 Apr;90(4):634-45.
18. Christiansen CL, Fields T, Lev G, Stephenson RO, Stevens-Lapsley JE. Functional Outcomes After the Prosthetic Training Phase of Rehabilitation After Dysvascular Lower Extremity Amputation. PM R. 2015 Nov;7(11):1118-26.
19. Sansam K, Neumann V, O'Connor R, Bhakta B. Predicting walking ability following lower limb amputation: a systematic review of the literature. J Rehabil Med. 2009 Jul;41(8):593-603.
20. Updated guidlines complex regional pain sysdrome type I [Internet]. 2014: Netherlands Society of Anaesthesiologists,Netherlands Society of Rehabilitation Specialists; 2014 []. Available from: http://www.posttraumatischedystrofie.nl/pdf/Executive_summary_guideline_CRPS_I_2014_docx.pdf.
21. Canavarro MC, Pereira M. Factor structure and psychometric properties of the European Portuguese version of a questionnaire to assess quality of life in HIV-infected adults: the WHOQOL-HIV-Bref. AIDS Care. 2012;24(6):799-807.
22. Masthoff ED, Trompenaars FJ, Van Heck GL, Hodiamont PP, De Vries J. Validation of the WHO Quality of Life assessment instrument (WHOQOL-100) in a population of Dutch adult psychiatric outpatients. Eur Psychiatry. 2005 Nov;20(7):465-73.
23. Development of the World Health Organization WHOQOL-BREF quality of life assessment. The WHOQOL Group. Psychol Med. 1998 May;28(3):551-8.
24. Connor KM, Davidson JR. Development of a new resilience scale: the Connor-Davidson Resilience Scale (CD-RISC). Depress Anxiety. 2003;18(2):76-82.
25. Spinhoven P, Ormel J, Sloekers PP, Kempen GI, Speckens AE, Van Hemert AM. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. Psychol Med. 1997 Mar;27(2):363-70.
26. Pallant JF, Bailey CM. Assessment of the structure of the Hospital Anxiety and Depression Scale in musculoskeletal patients. Health Qual Life Outcomes. 2005 Dec 19;3:82.
27. Derogatis LR. Symptom Checklist-90-R (SCL-90-R): administration, scoring and procedures manual. 3rd ed. ed. Minneapolis: ; NCS Pearson, Inc. 1994.
28. Arrindell WA EJ. Manual for a multidimensional psychopathology-indicator. Swets Test Publishers, Lisse: ; 2003.
29. Kendrick DB, Strout TD. The minimum clinically significant difference in patient-assigned numeric scores for pain. Am J Emerg Med. 2005 Nov;23(7):828-32.
30. Evers AW, Kraaimaat FW, Geenen R, Jacobs JW, Bijlsma JW. Pain coping and social support as predictors of long-term functional disability and pain in early rheumatoid arthritis. Behav Res Ther. 2003 Nov;41(11):1295-310.
31. Jamison RN, Virts KL. The influence of family support on chronic pain. Behav Res Ther. 1990;28(4):283-7.
32. Williams RM, Ehde DM, Smith DG, Czerniecki JM, Hoffman AJ, Robinson LR. A two-year longitudinal study of social support following amputation. Disabil Rehabil. 2004 Jul 22-Aug 5;26(14-15):862-74.

33. Hanley MA, Jensen MP, Ehde DM, Hoffman AJ, Patterson DR, Robinson LR. Psychosocial predictors of long-term adjustment to lower-limb amputation and phantom limb pain. Disabil Rehabil. 2004 Jul 22-Aug 5;26(14-15):882-93.
34. Bean DJ, Johnson MH, Heiss-Dunlop W, Lee AC, Kydd RR. Do psychological factors influence recovery from complex regional pain syndrome type 1? A prospective study. Pain. 2015 Nov;156(11):2310-8.
35. Geertzen JH, de Bruijn-Kofman AT, de Bruijn HP, van de Wiel HB, Dijkstra PU. Stressful life events and psychological dysfunction in Complex Regional Pain Syndrome type I. Clin J Pain. 1998 Jun;14(2):143-7.
36. Beerthuizen A, Stronks DL, Huygen FJ, Passchier J, Klein J, Spijker AV. The association between psychological factors and the development of complex regional pain syndrome type 1 (CRPS1)--a prospective multicenter study. Eur J Pain. 2011 Oct;15(9):971-5.
37. Neal LA. Complex regional pain syndrome: the role of the psychiatrist as an expert witness. Med Sci Law. 2009 Oct;49(4):241-6.
38. Pechtel P, Pizzagalli DA. Effects of early life stress on cognitive and affective function: an integrated review of human literature. Psychopharmacology (Berl). 2011 Mar;214(1):55-70.
39. Santarelli S, Zimmermann C, Kalideris G, Lesuis SL, Arloth J, Uribe A, et al. An adverse early life environment can enhance stress resilience in adulthood. Psychoneuroendocrinology. 2017 Feb 7;78:213-21.
40. Seery MD, Holman EA, Silver RC. Whatever does not kill us: cumulative lifetime adversity, vulnerability, and resilience. J Pers Soc Psychol. 2010 Dec;99(6):1025-41.
41. Stewart DE, Yuen T. A systematic review of resilience in the physically ill. Psychosomatics. 2011 May-Jun;52(3):199-209.
42. Oken BS, Chamine I, Wakeland W. A systems approach to stress, stressors and resilience in humans. Behav Brain Res. 2015 Apr 1;282:144-54.
43. Bodde MI, Schrier E, Krans HK, Geertzen JH, Dijkstra PU. Resilience in patients with amputation because of Complex Regional Pain Syndrome type I. Disabil Rehabil. 2014;36(10):838-43.
44. Allen G, Galer BS, Schwartz L. Epidemiology of complex regional pain syndrome: a retrospective chart review of 134 patients. Pain. 1999 Apr;80(3):539-44.
45. Sarrami P, Armstrong E, Naylor JM, Harris IA. Factors predicting outcome in whiplash injury: a systematic meta-review of prognostic factors. J Orthop Traumatol. 2017 Mar;18(1):9-16.
46. Ciccone DS, Bandilla EB, Wu W. Psychological dysfunction in patients with reflex sympathetic dystrophy. Pain. 1997 Jul;71(3):323-33.
47. Wampold BE. How important are the common factors in psychotherapy? An update. World Psychiatry. 2015 Oct;14(3):270-7.
48. Price DD, Finniss DG, Benedetti F. A comprehensive review of the placebo effect: recent advances and current thought. Annu Rev Psychol. 2008;59:565-90.

CHAPTER 7

Quality of life following amputation because of longstanding therapy-resistant complex regional pain syndrome type I

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Abstract

Background: Amputation as a treatment for long-standing, therapy-resistant complex regional pain syndrome type I (CRPS-I) is controversial. The aim of this study was to evaluate the long-term outcomes of amputation in patients with long-standing, therapy-resistant CRPS-I regarding quality of life, pain, recurrence of CRPS-I, use of a prosthesis, and functioning in daily life.
Methods: From May 2000 to September 2015, 53 patients underwent amputation of a limb affected by long-standing, therapy-resistant CRPS-I at our hospital. Forty-eight patients (40 women, 8 men) participated in this study. One participant participated only in the interview, because of health issues. Median age at the time of diagnosis was 33.5 years (interquartile range (IQR): 20.3 to 40.0 years), and median time interval between amputation and participation in this study was 5.5 years (IQR: 3.0 to 11.0 years). Participants completed 5 questionnaires; participated in a semi-structured interview; and, if indicated, underwent a physical examination. A longitudinal follow-up could be performed in a subgroup of 17 participants because their data were available from a previous study.
Results: Thirty-seven participants (77%) reported an important improvement in mobility after amputation (95% Confidence Interval (CI): 63 to 87). An important reduction of pain was reported by 35 participants after amputation (73%; 95% CI: 59 to 83). Twenty patients (42%; 95% CI: 29 to 56) reported important deteriorations (ranging from 1 to 11 important deteriorations per participant, IQR: 0.0 to 3.0). Deterioration of mobility was reported by 2 participants and deterioration of pain by 8 participants. CRPS-I recurred in 4 out of 47 participants (9%; 95% CI: 3 to 20). It recurred in the residual limb of 1 participant and in another limb of 3 participants.
Longitudinal follow-up of a subgroup (n=17) of participants showed no significant deteriorations.
Conclusion: Amputation should be considered as a treatment option for patients with long-standing, therapy resistant CRPS-I because it can increase mobility and reduce pain, thereby improving the quality of patients' lives.

Background

Complex regional pain syndrome type I (CRPS-I) is characterized by pain that is disproportionate to the inciting event. Other symptoms include sensory, sympathetic, motor, and trophic changes [1-3]. The syndrome often requires long and intensive treatment [4-6], including physical therapy, occupational therapy, pharmaceutical therapy, comprehensive multidisciplinary therapy, and/or neuromodulation [7, 8]. The pathophysiology is not yet understood [3, 9]. Within 6 to 13 months of onset, symptoms improve considerably in many patients [10]. However, in a small number of patients, CRPS-I might become therapy-resistant (not responding to medical treatment, physical therapy, occupational therapy, or multidisciplinary therapy, as recommended in the Dutch Guidelines) [7, 8]. Subsequently, patients might express the wish for amputation of the affected limb because of severe or unbearable pain, infections, or extremely limited mobility [7, 8, 11-13]. Nevertheless, amputation as a

treatment for long-standing therapy-resistant CRPS-I remains controversial [7, 8, 14, 15]. The procedure is irreversible, associated with surgery-related complications, and may result in phantom pain. Furthermore, CRPS-I can recur in the residual limb or somewhere else, for instance, in the opposite limb. Recently, a comparison was made between CRPS-I patients with and without amputation, and clinically relevant improvements were observed in all outcome measures in the amputation group [16]. Limited data exist on the long-term effects of amputation as a treatment for long-standing, therapy-resistant CRPS-I. Furthermore, little is known about the course of patients' functioning following amputation. Therefore, the aim of this study was to gain insight into the long-term outcomes of amputation in patients with CRPS-I regarding quality of life, pain, recurrence of CRPS-I, use of a prosthesis, and functioning in daily life. The current study follows up on previous research [14] and includes a larger study population, has a longer follow-up time, and allows for a longitudinal evaluation of outcomes in a subgroup.

Methods

The current study used a mixed ambispective design for performing quantitative and qualitative explorative analyses.
Fifty-three adult patients underwent amputation of a limb affected by long-standing, therapy-resistant CRPS-I at the University Medical Center Groningen (UMCG) between May 2000 to September 2015.
Patients were referred to our outpatient rehabilitation clinic for 2 reasons: they were suffering from long-standing CRPS-I despite earlier treatment, and they had strongly expressed the wish for amputation to their own physician. Prior to amputation, CRPS-I was diagnosed at our outpatient rehabilitation clinic, according to criteria of the International Association for the Study of Pain (IASP) [17] and criteria described by Bruehl et al. [1]. The Budapest criteria were used from 2012 onwards [18, 19]. Amputation was performed because of unbearable and therapy-resistant pain, life-threatening infections, or poor mobility. For instance, patients experienced their affected limb as an obstacle, were afraid to bump the limb, and expected to improve function and mobility without the limb. Within rehabilitation medicine, mobility is considered as the ability to move or be moved freely and easily with or without aids (wheelchairs, prostheses, orthoses, canes, crutches, and so forth). CRPS-I was considered therapy-resistant if it persisted despite earlier treatment according to Dutch guidelines [7]. First, patients who asked for an amputation were extensively screened by a multidisciplinary team to determine whether amputation could be a treatment option [12, 14]. This screening included an evaluation of whether all evidence-based treatments had been tried. The screening procedure and decision-making process have been described previously [15, 20].
An invitation letter to participate in this follow-up study was sent to all 53 patients. Twenty- one patients of these 53 had also participated in the previous study [14]. Data of this subgroup were used to compare characteristics with the group of participants amputated more recently. Additionally, this subgroup was used for the longitudinal evaluation. Participants could return the informed consent forms using the included prepaid envelope. Once written informed consent was obtained, a link to

a secure website was sent to the participants where they could fill out questionnaires online (a paper version was sent if preferred) and a semi-structured interview was scheduled.
A total of 5 questionnaires were filled out by the participants. The World Health Organization Quality of Life-BREF (WHOQOL-BREF) was used to assess quality of life [21]. It is divided into 4 domains: physical health (7 items), psychological (6 items), social relationships (3 items), and environment (8 items) [21]. Domain scores range from 4 to 20. Low scores indicate a poor quality of life. The internal consistency is good for all domains, except for the social domain, which is marginal [22]. The Connor-Davidson Resilience Scale (CD-RISC) was employed to assess resilience, using 25 items [23]. Higher scores indicate better resilience. Internal consistency is good for the full scale, and the CD-RISC has good psychometric properties [24]. The Hospital Anxiety and Depression Scale (HADS) was used to assess the severity of anxiety and depression symptoms [25, 26]. The internal consistency is adequate for both scales [27]. Scores above 8 indicate a possible anxiety disorder or depression. The depression subscale was part of the semi-structured interview. The Trinity Amputation and Prosthesis Experience Scales-Revised (TAPES-R) was used to assess the psychosocial processes involved in adjusting to a prosthesis [28]. This is a 64-item questionnaire divided into 4 sections: psychosocial adjustment; activity restriction; satisfaction with the prosthesis; and exploration of phantom limb pain, residual limb pain, and other medical conditions not related to the amputation. All scales and subscales show acceptable internal consistency [28]. We used the scores on the TAPES-R to determine the level of activity for lower limb amputee patients who use a prosthesis and converted this level into a corresponding K-level [29]. The Symptom Checklist-90-Revised (SCL-90-R) was used to assess psychological distress [30]. All 90 items are rated on a 5-point scale over the last 4 weeks. The internal consistency of the total scale is excellent [31]. Higher scores represent more psychological distress. Time required to fill out all questionnaires was estimated at 60 minutes per participant. Filled out questionnaires were included in the study up until January 1, 2017.
Semi-structured interviews were conducted by telephone by a physician (J.S.) in the presence of a psychologist (E.S.), who acted as an observer. Participants were informed about the presence of an observer, but the identity of the observer was masked. Prior to the start of the interview, participants were reassured that the collected data would be handled confidentially, as mentioned in the invitation letter. The interviews were recorded digitally. Additionally, answers were recorded on paper by the physician and psychologist. Results were compared afterwards. In case of disagreement, discussion followed and the recorded interview was replayed to reassess the interpretation of the interview.
Participants were asked to rate perceived changes (comparing the current post-amputation situation to the situation prior to amputation) on a 5-point Likert scale. Changes concerned pain, mobility, self-care, household tasks, job participation, hobbies, sport activities, social interaction, intimacy, mood, appearance, worrying, sleep, use of pain medication, self-confidence, and the general situation after amputation (Appendix 1). Furthermore, participants were asked to score the presence and intensity of the least and worst residual limb pain, phantom

sensations, and phantom pain in the last 2 weeks (0 = no pain, 10 = worst imaginary pain). Finally, some open questions, for example, regarding complaints if the participant suspected recurrence of CRPS-I, were asked. Interviews were completed in 30 to 60 minutes. If recurrence of CRPS-I was reported by the participant, an appointment was made for a physical examination by the physician (J.S.), in which the Budapest criteria were applied [18]. This physical examination was performed at the participant's home or in a hospital nearby, depending on the participant's preference. The research protocol was approved by the local Medical Research Ethics Committee, provided that only patients aged 18 years or older were included (METc 2015/561).

Statistical analyses

First, data were anonymized. Data analysis was performed with IBM SPSS Statistics for Windows (version 23.0, IBM Corp., Armonk, New York). Statistical significance was set a $p \leq 0.05$, unless stated otherwise. Descriptive statistics were used to report characteristics of the participants and the answers to the interview questions. Answers to the interview questions, scores on the TAPES-R, scores on the WHOQOL-BREF, and findings during the physical examinations were used as outcome measures. A sensitivity analysis was performed for measuring pain, mobility, and recurrence of CRPS-I. In the first analysis it was assumed that all participants who dropped out had the worst possible outcome (worst case scenario); in the second analysis it was assumed that all participants who dropped out had the best possible outcome (best case scenario). Additionally, scores on SCL-90-R, CD-RISC and HADS were used to describe the study population.

Mann-Whitney test was used to analyze differences between participants amputated before and after October 2008. Distribution of perceived changes (interview items) was analyzed with Chi-Square test to compare observed distribution with hypothesized distribution. One-sample t-test was used to analyze differences between mean scores on WHOQOL-BREF, SCL-90-R, CD-RISC, and HADS of our participants compared with norm data and control groups [31-35]. For the longitudinal analyses, paired samples t-test was used to asses differences between mean scores on WHOQOL-BREF and total score on SCL-90-R. Differences in scores on the TAPES-R were analyzed using the Wilcoxon Signed Ranks test.

Results

Of the 53 patients invited, 48 participated in this study (Table 1). One participant agreed to participate in the interview, but she (later) declined to fill out the questionnaires and undergo a physical examination because of health issues. She reported recurrence of CRPS-I in the residual leg, in the opposite leg, and in an arm, and she experienced pulmonary and abdominal health problems.

In the period of January 2010 to September 2015, the requests of 16 patients who requested an amputation were turned down. The main considerations were (more items per person are possible): criteria for CRPS-I were not met (n=6); patients did not have realistic expectations about outcomes of the amputation (n=4); not all treatments according to the Dutch guidelines had been tried [7] (n=4, of which 3 patients were advised to follow a multidisciplinary rehabilitation program and 1

patient was advised to try neuromodulation); the extremity was still functional (n=2); comorbidity negatively influenced possible outcomes (n=2); conversion (n=1); suspicion of CRPS-2 (n=1); and suspicion of auto-mutilation (n=1). Patients' requests that were turned down were not systematically recorded before 2010.

Table 1 Table of participation and non-participation at different time points.

Amputation request turned down (n)	T0 year	T0 (n)	T1 (2009) reasons not to participate	T1 (n)	T2 (2016) reasons not to participate	T2 (n)	T2# (2009 + 2016) reasons not to participate	T2# (n)
-	2000	1		1		1		1
-	2001	1		1	no contact (n=1)	0	no contact (n=1)	0
-	2002	1		1		1		1
-	2003	4		4		4	reported sick*	3
-	2004	6		6	deceased (n=2)	4	deceased (n=2)	4
-	2005	3	refused (n=1)	2		3	refused (n=1)	2
-	2006	1		1		1		1
-	2007	2		2		2		2
-	2008	4	< 18 (n=1)	3		4	<18 (n=1)	3
-	2009	3				3		
2	2010	2			deceased (n=1)	1		
2	2011	3				3		
2	2012	10			no contact (n=1)	9		
2	2013	6				6		
2	2014	1				1		
6	2015	5				5		
16	total	53		21		48		17

T0= year of amputation; T1= participants of previous research, data collection 2009; T2= participants in current research, data collection 2016; T2#= participants in current research with longitudinal follow-up: comparison between 2009 and 2016.
– no data available
* refused to fill out questionnaires and undergo physical examination after participating in the interview, because she was too sick and ceased participation.

When comparing characteristics of participants in the previous study with participants who had undergone an amputation more recently, a significant difference was found for age (median age 53.5 versus 44.5 years) and number of years after amputation (median time after amputation 11.5 versus 3.5 years). No other significant differences were found. (Tables 2 and 3). No significant differences were found between these two groups in outcomes with respect to the interview items, scores on questionnaires, and recurrence of CRPS-I (Appendix 2). Therefore, the 2 groups were joined together and further analyzed as one group. First, data of the total group will be presented (n=48), followed by a longitudinal analysis of the subgroup of participants who had already participated in the previous study (n=17) [14]. In most participants (n=20, 41%) trauma was the inciting event for developing CRPS-I, followed by some form of surgery (n=16, 34%; Table 2). Forty-three participants (90%) underwent a lower limb amputation. Thirty-five participants (81%)

with a lower limb amputation were fitted with a prosthesis (Table 3). Eleven participants did not use the prosthesis anymore at follow-up because of pain or fitting problems. Nineteen participants (40%) with a lower limb amputation used the prosthesis for 8 hours or more daily. Two participants with an upper limb amputation (1 transhumeral and 1 transradial amputation) were fitted with a prosthesis and both used the prosthesis 4 to 8 hours daily.

Table 2 Characteristics of participants amputated because of long-standing therapy-resistant CRPS-I (n=48).

Participant characteristics	**n (%)**
Age at time of diagnosis (years)	33.5 (20.3 to 40.0) ¥
Age at time of amputation (years)	41.0 (28.5 to 46.0) ¥
Interval between amputation and study (years)	5.5 (3.0 to 11.0) ¥
Female	40 (83)
Inciting event of CRPS-I	
Trauma	20 (42)
Surgery	10 (21)
Unknown/spontaneous	8 (17)
Arthroscopy	6 (13)
Overuse injury	2 (4)
Cast immobilization for tendonitis in the foot	1 (2)
Needle stick injury	1 (2)
Main reason for amputation #	
Severe or unbearable pain	48 (100)
Non-functional limb	48 (100)
Contractures	36 (75)
Wounds/infections	15 (31)
Level of amputation	
Transhumeral	3 (6)
Transradial	2 (4)
Transfemoral	9 (19)
Knee disarticulation	18 (38)
Transtibial	16 (33)

Percentages might not add up to 100% due to rounding off.
¥ Median (IQR).
Multiple reasons are possible

Recurrence of CRPS-I was reported by 22 participants (46%; 95% Confidence Interval (CI) 33 to 60). The diagnosis was confirmed by physical examination in 4 of 47 participants (9%; 95% CI: 3 to 20) after applying the Budapest criteria. One participant refused a physical examination. In the worst case scenario regarding recurrence of CRPS-I, 27 of 53 participants (51%; 95% CI: 38 to 64) would have self-reported recurrence and 10 of 53 participants (19%; 95% CI: 11 to 31) would have recurrence using the Budapest criteria. In the best case scenario regarding recurrence of CRPS-I, 22 of 53 participants (42%; 95% CI: 29 to 55) would have self-reported recurrence and 4 of 53 participants (8%; 95% CI: 3 to 18) would have recurrence using the Budapest criteria.
Self-reported residual limb recurrence of CRPS-I developed within 3.5 years (range 0 to 3.3 years), in 13 participants and self-reported recurrence elsewhere developed within 5 years in 4 of 6 participants (range 1.0 to 11.0 years; total n<22 due to missing values). Seven participants (15%) underwent a re-amputation because of recurrence of CRPS-I, of which 6 participants were re-amputated without consulting us. These re-amputations mostly took place in other hospitals. One participant had already undergone an amputation before the re-amputation in our center because of recurrence of CRPS-I in the same limb. Of these 7 participants, 2 (29%) still had

complaints and reported recurrence of CRPS-I elsewhere. Nine participants (19%) underwent re-surgery in the residual limb for other reasons than CRPS-I (e.g., adherent scars or bone spurs).

Table 3 Post amputation results (n=48).

Characteristics	n (%)
Fitted with a prosthesis	
Upper extremity	
Yes	2 (4)
No	3 (6)
Lower extremity	
Yes	24 (50)
No	6 (13)
Yes, but not using prosthesis anymore	11 (23)
Missing ¥	2 (4)
Period wearing a prosthesis	
Upper limb amputation	
Daily 8 hours or more	0 (0)
Daily 4 to 8 hours	2 (4)
Daily fewer than 4 hours	0 (0)
Few days a week	0 (0)
Never / not applicable	3 (6)
Missing ¥	0 (0)
Lower limb amputation	
Daily: 8 hours or more	19 (40)
Daily: 4 to 8 hours	5 (10)
Daily: fewer than 4 hours	0 (0)
Few days a week	0 (0)
Never / not applicable	17 (35)
Missing ¥	2 (4)
K-level (n=43)[27]	
K0	1 (2)
K1	2 (5)
K2	8 (19)
K3	9 (21)
K4	4 (9)
Not using prosthesis anymore	17 (40)
Missing¥	2 (5)
Recurrence of CRPS-I reported by patient	
In residual limb	7 (15)
Elsewhere	5 (10)
In residual limb and elsewhere	10 (21)
No recurrence	26 (54)
Recurrence of CRPS-I in residual limb according to Bruehl criteria	
In residual limb	4 (8)
Elsewhere	2 (4)
In residual limb and elsewhere	2 (4)
Missing #	1 (2)
Recurrence of CRPS-I in residual limb according to Budapest criteria	
In residual limb	1 (2)
Elsewhere	3 (6)
In residual limb and elsewhere	0 (0)
Missing #	1 (2)
Median (IQR) symptom free period (years) of residual limb in case of recurrence of CRPS-I reported by patient (n=13)	0.5 (0.0 to 1.5)
Median (IQR) symptom free period (years) elsewhere in case of recurrence of CRPS-I reported by patient (n=6)	2.3 (1.0 to 7.6)
Number of patients with re-amputation because of CRPS-IΩ	
Affected limb	1 (2)
Different limb	6 (13)
Number of patients with re-operation in residual limb because of other reasons*	9 (19)

Percentages might not add up to 100% due to rounding off.
¥ Missing because question was not filled in.

ת K-level rating system is used to indicate a lower limb amputee's potential to use a prosthetic device. K0=not possible to walk or make transfer, K1=able to make transfers, walk on an even surface with steady pace, K2=walk on an uneven surface, climbing stairs, K3=can handle all obstacles, walks with variable speed, K4= functions at top level in work and daily life.
Missing because patient declined physical examination.
Ω Two re-amputations were performed in our center (both knee disarticulations, one in the other limb, one after a previous transtibial amputation). One patient with an initial transradial amputation underwent a bilateral transtibial amputation.
* Extirpation of neuroma (n=3), prosthesis fitting problems (n=2), correction of abnormal residual limb position due to dystonia (n=1), pain due to protrusive femur (n=1) or impaired mobility and pain due to hypermobility of the patella (n=2). More than half of the patients underwent more than one procedure for these problems.

Perceived changes after amputation

Thirty-seven participants (77%) reported an important improvement in mobility (95% CI: 63 to 87, Table 4). An important reduction of pain was reported by 35 participants (73%; 95% CI: 59 to 83).

In the worst case scenario for mobility, 70% (95% CI: 56 to 80) of the participants would score an important improvement and for pain this would apply for 66% (95% CI: 53 to 77) of the participants. In the best case scenario for mobility, 79% (95% CI: 67 to 88) of the participants would score an important improvement and for pain this would apply for 75% (95% CI: 62 to 85) of the participants.

Table 4 Perceived changes after amputation (n=48).

	Important improvement n(%)	**Slight improvement n(%)**	**No change n(%)**	**Slight deterioration n(%)**	**Important deterioration n(%)**
Mobility	37 (77)	7 (15)	2 (4)	0 (0)	2 (4)
Overall change	35 (73)	5 (10)	2 (4)	1 (2)	5 (10)
Pain	35 (73)	2 (4)	3 (6)	2 (4)	6 (13)
Pain medication	25 (52)	5 (10)	9 (19)	2 (4)	7 (15)
Sleep	22 (46)	4 (8)	12 (25)	2 (4)	8 (17)
Hobbies	19 (40)	5 (10)	15 (31)	3 (6)	6 (13)
Washing/dressing	17 (35)	10 (21)	16 (33)	1 (2)	4 (8)
Sports	17 (35)	4 (8)	20 (42)	1 (2)	6 (13)
Household activities	16 (33)	10 (21)	12 (25)	4 (8)	6 (13)
Mood	13 (27)	5 (10)	25 (52)	1 (2)	4 (8)
Work	13 (27)	5 (10)	23 (48)	2 (4)	5 (10)
Self-confidence	13 (27)	3 (6)	21 (44)	4 (8)	7 (15)
Using a toilet	12 (25)	9 (19)	22 (46)	2 (4)	3 (6)
Social contacts	12 (25)	8 (17)	21 (44)	1 (2)	6 (13)
Appearance	11 (23)	7 (15)	21 (44)	4 (8)	5 (10)
Intimacy	8 (17)	4 (8)	23 (48)	4 (8)	9 (19)
Worrying	7 (15)	6 (13)	27 (56)	5 (10)	3 (6)
Feeling understood	6 (13)	7 (15)	27 (56)	3 (6)	5 (10)
Negative attention	4 (8)	5 (10)	30 (63)	4 (8)	5 (10)

The distribution of the perceived changes were all significantly different from the hypothesized distribution (Chi-Square test, $p \leq 0.05$). Percentages do not add up to 100% due to rounding off.

Post amputation, 45 participants (94%) reported 1 or more important improvements (ranging from 1 to 15 important improvements per participant; IQR: 3.0 to 8.8), and 20 participants (42%) reported 1 or more important deteriorations (ranging from 1 to 11 important deteriorations per participant; IQR: 0.0 to 3.0). Deterioration was reported most often for the items intimacy (n=13, 27%), self-confidence (n=11, 23%), household activities, and sleep (both n=10, 21%).

Experienced intensity and burden of residual limb pain and phantom pain are shown in Table 5.

Table 5 Experienced intensity and burden of residual limb pain and phantom pain.

	Little	Annoying	Alarming	Terrible	Unbearable
Intensity, n (%)					
-Residual limb pain (n=23/43)*	3 (13)	5 (22)	8 (35)	6 (26)	1 (4)
-Phantom pain (n=23/42)*	5 (22)	9 (39)	5 (22)	4 (17)	0 (0)
Burden, n (%)	None	Little	Moderate	Much	Very much
-Residual limb pain (n=23/43)*	3 (13)	4 (17)	8 (35)	5 (22)	3 (13)
-Phantom pain (n=22/42)*	6 (27)	5 (23)	6 (27)	3 (14)	2 (9)

* The numbers between brackets after indicate the number of participants experiencing residual limb pain or phantom pain, respectively, as well as the number of valid observations. n<48 due to missing values.

Results of WHOQOL-BREF, SCL-90-R, CD-RISC and HADS, compared with norm data and control groups are shown in Table 6.

Table 6 Results of WHOQOL-BREF, SCL-90-R, CD-RISC and HADS, compared with reference and control groups.

Questionnaire	Current study population	Dutch norm values[31-33]	Other control groups	Study population versus Dutch norm values	Study population versus other control groups
			Rehabilitation outpatients[34]		Rehabilitation outpatients[34]
WHOQOL-BREF# Domains	Mean (SD)	Mean (SD)	Mean (SD)	Difference (95%CI)	Difference (95% CI)
-Physical	12.7 (3.4)	15.2 (2.6)	11.0 (2.7)	-2.5 (-3.5 to -1.4)*	1.7 (0.7 to 2.8)*
-Psychological	14.8 (3.0)	14.4 (2.0)	13.6 (2.4)	-0.4 (-0.5 to -1.3)	1.2 (0.3 to 2.1)*
-Social	14.3 (3.3)	15.4 (2.9)	14.8 (3.4)	-1.1 (-2.1 to -0.2)*	-0.5 (-1.5 to 0.4)
-Environment	14.8 (2.7)	15.8 (2.0)	14.2 (2.2)	-1.0 (-1.8 to -0.2)*	0.6 (-0.2 to 1.4)
			Chronic pain patients[31]		Chronic pain patients[31]
SCL-90-R total score#	142.3 (48.9)	118.3 (32.4)	148.6 (45.5)	24.0 (9.6 to 38.3)*	-6.3 (-20.7 to 8.0)
			Rehabilitation outpatients[34]		Rehabilitation outpatients[34]
CD-RISC#	73.1 (15.7)	-	63.2(14.1)		9.9 (5.3 to 14.5)*
			Patients with phantom limb pain[35]		Patients with phantom limb pain[35]
HADS-A#	3.7 (3.5)	5.1 (3.6)	8.0 (3.9)	-1.4(-2.4to-.4)*	-4.3(-5.2 to -3.3)*
HADS-D	3.2 (4.0)	3.4 (3.3)	(5.5)	-0.2(-1.3 to1.0)	-4.5(-5.5 to -3.3)*

One-sample t-test was used, * P ≤ 0.05, 95% CI = 95% Confidence Interval, - no data available, # n=47 because 1 participant declined to fill out the questionnaires

Prior to the amputation, a subgroup consisting of the last 31 participants included in the study was asked to score how much pain was experienced on a NRS scale ranging from 0 (no pain) to 10 (worst pain imaginary). The same question was repeated during the interview (median 4.0 years after the amputation; IQR: 2.0 to 5.0 years). In this subgroup of 31 participants, a significant decrease in pain of 3.5 points (SD 3.3) was found.

Satisfaction with decision for amputation

Out of the 48 participants in this study, 47 (98%) would again choose an amputation under the same circumstances. One participant would not choose amputation again. In her case, a life-threatening infection was the primary reason for a lower limb amputation.

Longitudinal follow-up

Longitudinal analysis of the 17 participants who had already participated in the previous study showed no significant differences regarding interview outcomes (interview items in accordance with Table 4, participation ,decision-making process, and self-reported recurrence; data not shown, available on request), median scores of the WHOQOL-BREF, and median total score on the SCL-90-R.

Table 7 Changes over time in questionnaires outcomes in patients who underwent an amputation for CRPS-I (n=17).

Questionnaire	**Outcomes previous study[14]**					**Current evaluation**					
WHOQOL-BREF (n=16)	Median (IQR)					Median (IQR)					p
Physical domain	13.7 (10.9 to 15.9)					13.1 (13.1 to 16.1)					0.990
Psychological domain	14.7 (14.0 to 16.5)					15.3 (13.7 to 16.7)					0.850
Social domain	14.7 (12.3 to 18.7)					15.3 (10.3 to 17.1)					0.234
Environment domain	14.5 (11.3 to 16.3)					15.0 (13.5 to 16.9)					0.062
SCL-90-R (n=16)											
Psychoneuroticism score	127.5 (104.8 to 157.3)					129.0 (112.3 – 162.5)					0.403
TAPES-R	Distribution of answer options					Distribution of answer options					
Experienced burden of: ¥	N	L	Mo	Mu	VM	N	L	Mo	Mu	VM	
Phantom sensations	4	4	5	3	1	8	7	1	0	1	0.040*
Residual limb pain (n=13)	3	1	5	1	3	9	2	1	1	0	0.001*
Phantom pain (n=12)	1	3	4	2	2	8	3	1	0	0	0.001*
Fitted with a a prosthesis	n = 12					n = 11					1.000
Period wearing a prosthesis #	>8	4-8	<4	Fd	N	> 8	4-8 1	<4 0	Fd 0	N 2	0.672
	11	0	0	0	1						

Wilcoxon Signed Ranks test was used. *p ≤ 0.05 was considered significant. n<17 due to missing values.
¥ N: none, L: little, Mo: moderate, Mu: much, VM: very much.
>8: daily 8 hours or more, 4-8: daily 4 to 8 hours, <4: daily fewer than 4 hours, Fd: a few days in a week, N: never.

In this study, the experienced burden of phantom sensations, residual limb pain, and phantom pain was significantly less compared with results from the previous study [14]. Post-hoc analysis of the intensity of residual limb and phantom pain showed that 2 participants still experienced alarming to terrible residual limb pain, and 2 participants still experienced alarming phantom pain. No participants still experienced unbearable residual limb or phantom pain. No significant difference was found regarding prosthesis use. Fewer participants seemed to wear their prosthesis (9 participants in current study versus 11 participants in the previous study); however, this difference was not significant.

Discussion

Approximately 75% of the participants perceived important improvements in mobility and pain after the amputation. Self-reported recurrence of the CRPS-I occurred in

approximately 50% of the participants, but was confirmed in only 9% of the participants after applying the Budapest criteria. The improvement in mobility while performing specific activities (e.g., using a toilet, performing hobbies/sports, or participating at work) could not be generalized to all activities. General symptoms such as worrying, mood, and negative attention did not change for the most part. Forty-two percent of participants reported 1 or more important deteriorations. Analysis of deterioration related to specific activities showed it occurred in fewer than 30% of participants. The above reported results are relevant because treatment options for therapy-resistant CRPS-I are scarce, and patients suffer immensely [13]. Pain reduction was the main goal of most participants, and 35 participants (73%) did experience an important improvement regarding pain. The extent of improvement in pain found in this study appears to contrast with another study on amputation in CRPS-I patients, in which only 11 participants (32%) experienced pain relief [11]. This difference may be partly explained by the fact that our study assessed improvement instead of relief. The average decrease in pain, measured in a subgroup of the last 31 participants who underwent amputation, was 3.5 points (SD 3.3) on the NRS scale. This difference is comparable with the 3.2 point difference between amputee and non-amputee patients with CRPS-I found in another study and is clinically relevant [16].

The second goal mentioned by participants was an increase in mobility. Thirty-seven participants (77%) reported an important increase in mobility. When asked for specific activities that require mobility, fewer participants experienced improvement and more experienced deterioration. For some activities, the discrepancy between general improvement in mobility and perceived deterioration of one specific activity is explainable. For example, participants mentioned disappointments due to difficulties donning and doffing their prosthesis in the restroom, but they still experienced a general improvement in mobility because they could walk with a prosthesis. Furthermore, wheelchair mobility may be experienced as improved because participants' fear of bumping the affected limb decreased or disappeared altogether. Improved wheelchair mobility may also explain the discrepancy between improvement in general mobility and the relatively low number of participants using a prosthesis. The discrepancies between general improvement in mobility and deterioration of mobility related to work, hobbies, and sports are more difficult to explain. Poor social acceptance of disabled persons in work and leisure activities might explain part of the discrepancies.

A striking deterioration was seen for the items self-confidence (n=11, 23%) and intimacy (n=13, 27%) post amputation. Negative effects of an amputation on social function and intimacy have been reported previously [36, 37]. These effects might be linked to perceived appearance. Deterioration of appearance in relation to the reported deterioration of intimacy was analyzed in a post-hoc analysis. Only 4 of the 13 participants (31%) who reported deterioration of intimacy also reported deterioration of appearance.

Although quality of life did not meet Dutch norm standards, it did exceed standards for rehabilitation outpatients. The difference with the Dutch norm standards is only of clinical importance for the physical domain and can be explained by the amputation

and by the fact that after recovery from CRPS-1 residual symptoms may still be present [38].
Twenty-two participants (46%) reported some kind of recurrence (pain, in combination with sensory, and/or sympathetic ,and/or motor, and/or trophic changes). This finding is in contrast with the 35 participants (73%) who reported an important improvement in pain. Based on the physical examination, the physician found recurrence of CRPS-I in 4 participants (9%) after applying the Budapest criteria. The CRPS-I diagnosis was not warranted in most cases because the fourth criterion ('there is no other diagnosis that better explains the patient's signs and symptoms') was not met. Reported and objectified symptoms could be explained by another condition, for example, a neuroma. Furthermore, in many cases not enough symptoms were present during the physical examination to meet all 4 of the Budapest criteria.
In a systematic review, recurrence of CRPS-I was reported in 34 of 65 participants (52%); however, the criteria used for the diagnosis of recurrence were not reported in the source studies [12]. The outcomes reported in this review are in line with our results for self-reported recurrence. Although our results regarding established recurrence may seem reassuring, drop out could have biased the study's outcomes. In the worst case scenario, the total number of recurrences (Budapest criteria) would be 10 out of 53 participants (19%). Forty-seven participants (98%) would choose an amputation again under the same circumstances. This outcome is very positive, but it could be influenced by cognitive dissonance. The theory of cognitive dissonance predicts that in case of an irrevocable choice, people try to minimize regret [39]. An amputation cannot be reversed; therefore, instead of regretting this decision, it feels better to think it was the best choice.
The low mean scores on the depression and anxiety scale after amputation are remarkable. Another study found that especially anxiety and pain-related fear were associated with poor outcomes in CRPS-I patients [40]. Anxiety and pain-related fear tended to decrease after 1 year in that study (by that time most patients had fewer symptoms than at the start of the CRPS-I). It is possible that the amputation was a relief or that patients who were motivated to undergo the amputation had lower scores on depression and anxiety prior to the amputation.
Most self-reported recurrences developed in the first 5 years. In 2 participants CRPS-I recurred elsewhere in the body after the first 5 years.
The average age of the participants in this study was lower than the age of the average CRPS-I patient in the Netherlands as reported by De Mos et al. [41]. They reported the highest incidence in females aged 61 to 70 years and found that the upper extremity was more often affected than the lower extremity [41]. This age difference could be related to the severity of CRPS-I. In our study, only patients with long-standing, therapy-resistant CRPS-I who were motivated to undergo an amputation were seen, whereas the other study is a cohort of all CRPS-I patients recorded in a general practice research database over a 9-year period. In a systematic review of 26 papers describing 107 patients who underwent an amputation for long-standing therapy-resistant CRPS-I, a mean age of 40.3 years was found (based on part of the studies). Additionally, lower limb amputations were reported twice as often as upper limb amputations [12]. Our participants are better

comparable with those included in this review [12] than with the patients with CRPS-I recorded in a general practice research database.
In the longitudinal analysis (n=17), no significant differences were found regarding prosthesis use; this remained stable over 7 years. A slight but significant improvement was found in residual limb and phantom pain. The improvement in phantom pain has been reported in other research as well [42]

Study strengths

A strength of the current study was the relatively large number of participants. Compared with the previous study in 2012, twice as many participants were included. Furthermore, a longitudinal follow-up of a subgroup of 17 participants who had already participated in the previous study in 2012 could be performed [14]. Follow-up time increased for this subgroup, which meant that insight could be gained into the stability of long-term outcomes after amputation for long-standing therapy-resistant CRPS-I

Study limitations

This study lacked a control group of patients with longstanding therapy resistant CRPS-I who did not undergo an amputation. Nevertheless, it was possible to compare our data with norm values.
Only patients with an amputation were included. Therefore, no insight into quality of life and functioning of patients who were refused an amputation could be gained. We realize that our participants form an unusual and small subgroup of patients. Also, during the period this study was conducted, the diagnostic criteria for CRPS-I changed, making interpretation of diagnosis and recurrence difficult. We therefore decided to apply the most recent criteria to determine recurrence, although even these criteria (the Budapest criteria) are under scrutiny. Some critics claim that CRPS-I is not a disease, that overlap exists with other diseases, and that the validity of the criteria is not sufficient and not tested thoroughly [43-45].
Furthermore, the follow-up time was relatively long for many participants, which could have resulted in recall bias when assessing the situation prior to the amputation. Most participants reported improvement or no changes, which may reflect that they felt they 'had to' report positive outcomes to justify the amputation. Although the success rate of 75% is notable, it is not proven that an amputation caused the positive change, nor is it clear why the situation of some participants deteriorated after the amputation.

Conclusion

Approximately 75% of the participants in this study experienced a clinically relevant improvement in mobility and a reduction of pain. The average pain reduction, based on the subgroup of 31 participants, was 3.5 points on a 0-10 scale. Some participants experienced residual symptoms of the CRPS-I and impediments because of the amputation. Therefore, it is important to extensively screen patients to assess whether their post-amputation expectations and goals are realistic. For patients with long-standing, therapy resistant CRPS-I, amputation should be considered as a treatment option because it can increase mobility and reduce pain, which positively affects the quality of patients 'lives.

References

1. Bruehl S, Harden RN, Galer BS, Saltz S, Bertram M, Backonja M, Gayles R, Rudin N, Bhugra MK, Stanton-Hicks M. External validation of IASP diagnostic criteria for Complex Regional Pain Syndrome and proposed research diagnostic criteria. International Association for the Study of Pain. Pain. 1999;81(1-2):147-154.
2. de Mos M, Sturkenboom MC, Huygen FJ. Current understandings on complex regional pain syndrome. Pain Pract. 2009;9(2):86-99.
3. Maihofner C, Seifert F, Markovic K. Complex regional pain syndromes: new pathophysiological concepts and therapies. Eur J Neurol. 2010;17(5):649-660.
4. Geertzen JH, Dijkstra PU, van Sonderen EL, Groothoff JW, ten Duis HJ, Eisma WH. Relationship between impairments, disability and handicap in reflex sympathetic dystrophy patients: a long-term follow-up study. Clin Rehabil. 1998;12(5):402-412.
5. Tran DQH, Duong S, Bertini P, Finlayson RJ. Treatment of complex regional pain syndrome: a review of the evidence. Can J Anaesth. 2010 Feb;57(2):149-166.
6. O'Connell NE, Wand BM, McAuley J, Marston L, Moseley GL. Interventions for treating pain and disability in adults with complex regional pain syndrome. Cochrane Database Syst Rev. 2013; doi(4):CD009416.
7. Perez RSGM, Geertzen, J.H.B. Dijkstra P.U. Dirckx M. Updated guidlines complex regional pain sysdrome type I. 2014. http://www.posttraumatischedystrofie.nl/pdf/Executive_summary_guideline_CRPS_I_2014_docx.pdf. Accessed Jan 2 2017.
8. Perez RS, Zollinger PE, Dijkstra PU, Thomassen-Hilgersom IL, Zuurmond WW, Rosenbrand KC, Geertzen JH, CRPS I task force. Evidence based guidelines for complex regional pain syndrome type 1. BMC Neurol. 2010;10:20-2377-10-20.
9. Marinus J, Moseley GL, Birklein F, Baron R, Maihofner C, Kingery WS, van Hilten JJ. Clinical features and pathophysiology of complex regional pain syndrome. Lancet Neurol. 2011;10(7):637-648.
10. Bean DJ, Johnson MH, Kydd RR. The outcome of complex regional pain syndrome type 1: a systematic review. J Pain. 2014;15(7):677-690.
11. Dielissen PW, Claassen AT, Veldman PH, Goris RJ. Amputation for reflex sympathetic dystrophy. J Bone Joint Surg Br. 1995;77(2):270-273.
12. Bodde MI, Dijkstra PU, den Dunnen WF, Geertzen JH. Therapy-resistant complex regional pain syndrome type I: to amputate or not? J Bone Joint Surg Am. 2011;93(19):1799-1805.
13. Goebel A, Barker C, Turner-Stokes L, et al. Complex regional pain syndrome in adults: UK guidelines for diagnosis, referral and management in primary and secondary care. London: RCP, 2018. 2018. https://www.rcplondon.ac.uk/guidelines-policy/complex-regional-pain-syndrome-adults. Accessed 09-17 2018.
14. Krans-Schreuder HK, Bodde MI, Schrier E, Dijkstra PU, van den Dungen JA, den Dunnen WF, Geertzen JH. Amputation for long-standing, therapy-resistant type-I complex regional pain syndrome. J Bone Joint Surg Am. 2012;94(24):2263-2268.
15. Bodde MI, Dijkstra PU, Schrier E, van den Dungen JJ, den Dunnen WF, Geertzen JH. Informed Decision-Making Regarding Amputation for Complex Regional Pain Syndrome Type I. J Bone Joint Surg Am. 2014;96(11):930-934.

16. Midbari A, Suzan E, Adler T, Melamed E, Norman D, Vulfsons S, Eisenberg E. Amputation in patients with complex regional pain syndrome: a comparative study between amputees and non-amputees with intractable disease. Bone Joint J. 2016;98-B(4):548-554.
17. Merskey H BN. Classification of chronic pain: descriptions of chronic pain syndromes and definitions of pain terms. 2nd ed. ed. Seattle; 1994.
18. Harden RN, Bruehl S, Stanton-Hicks M, Wilson PR. Proposed new diagnostic criteria for complex regional pain syndrome. Pain Med. 2007;8(4):326-331.
19. Harden RN, Bruehl S, Perez RS, Birklein F, Marinus J, Maihofner C, Lubenow T, Buvanendran A, Mackey S, Graciosa J, Mogilevski M, Ramsden C, Chont M, Vatine JJ. Validation of proposed diagnostic criteria (the "Budapest Criteria") for Complex Regional Pain Syndrome. Pain. 2010;150(2):268-274.
20. Schrier E, Dijkstra PU, Zeebregts CJ, Wolff AP, Geertzen JHB. Decision making process for amputation in case of therapy resistant complex regional pain syndrome type-I in a Dutch specialist centre. Medical Hypotheses. 2018;121:15-20; doi:https://doi.org/10.1016/j.mehy.2018.08.026.
21. Skevington SM, Lotfy M, O'Connell KA, WHOQOL Group. The World Health Organization's WHOQOL-BREF quality of life assessment: psychometric properties and results of the international field trial. A report from the WHOQOL group. Qual Life Res. 2004;13(2):299-310.
22. Canavarro MC, Pereira M. Factor structure and psychometric properties of the European Portuguese version of a questionnaire to assess quality of life in HIV-infected adults: the WHOQOL-HIV-Bref. AIDS Care. 2012;24(6):799-807.
23. Connor KM, Davidson JR. Development of a new resilience scale: the Connor-Davidson Resilience Scale (CD-RISC). Depress Anxiety. 2003;18(2):76-82.
24. Windle G, Bennett KM, Noyes J. A methodological review of resilience measurement scales. Health Qual Life Outcomes. 2011;9:8-7525-9-8.
25. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67(6):361-370.
26. Aylard PR, Gooding JH, McKenna PJ, Snaith RP. A validation study of three anxiety and depression self-assessment scales. J Psychosom Res. 1987;31(2):261-268.
27. Pallant JF, Bailey CM. Assessment of the structure of the Hospital Anxiety and Depression Scale in musculoskeletal patients. Health Qual Life Outcomes. 2005;3:82.
28. Gallagher P, MacLachlan M. Development and psychometric evaluation of the Trinity Amputation and Prosthesis Experience Scales (TAPES). Rehabil Psychol. 2000;45(2):130-154.
29. Medical Function Classification Level (MFCL). Health care financing administration. HCFA common procedure coding system HCPCS. Washington, DC: US Government Printing Office, 2001, ch. 5.3.
30. Derogatis LR. Symptom Checklist-90-R (SCL-90-R): administration, scoring and procedures manual. 3rd ed. ed. Minneapolis: ; NCS Pearson, Inc. 1994.
31. Arrindell WA EJ. Manual for a multidimensional psychopathology-indicator: Swets Test Publishers, Lisse; 2003.

32. Schrier E, Schrier I, Geertzen JH, Dijkstra PU. Quality of life in rehabilitation outpatients: normal values and a comparison with the general Dutch population and psychiatric patients. Qual Life Res. 2016;25(1):135-142.
33. Spinhoven P, Ormel J, Sloekers PP, Kempen GI, Speckens AE, Van Hemert AM. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. Psychol Med. 1997;27(2):363-370.
34. Masthoff ED, Trompenaars FJ, Van Heck GL, Hodiamont PP, De Vries J. Validation of the WHO Quality of Life assessment instrument (WHOQOL-100) in a population of Dutch adult psychiatric outpatients. Eur Psychiatry. 2005;20(7):465-473.
35. Kazemi H, Ghassemi S, Fereshtehnejad SM, Amini A, Kolivand PH, Doroudi T. Anxiety and depression in patients with amputated limbs suffering from phantom pain: a comparative study with non-phantom chronic pain. Int J Prev Med. 2013;4(2):218-225.
36. Woods AJ, Mark VW, Pitts AC, Mennemeier M. Pervasive cognitive impairment in acute rehabilitation inpatients without brain injury. PM R. 2011;3(5):426-432.
37. Verschuren JE, Geertzen JH, Enzlin P, Dijkstra PU, Dekker R. Sexual functioning and sexual well-being in people with a limb amputation: a cross-sectional study in the Netherlands. Disabil Rehabil. 2016;38(4):368-373.
38. Deans SA, McFadyen AK, Rowe PJ. Physical activity and quality of life: A study of a lower-limb amputee population. Prosthet Orthot Int. 2008;32(2):186-200.
39. Homer JJ, Sheard CE, Jones NS. Cognitive dissonance, the placebo effect and the evaluation of surgical results. Clin Otolaryngol Allied Sci. 2000;25(3):195-199.
40. Bean DJ, Johnson MH, Heiss-Dunlop W, Lee AC, Kydd RR. Do psychological factors influence recovery from complex regional pain syndrome type 1? A prospective study. Pain. 2015;156(11):2310-2318.
41. de Mos M, de Bruijn AG, Huygen FJ, Dieleman JP, Stricker BH, Sturkenboom MC. The incidence of complex regional pain syndrome: a population-based study. Pain. 2007;129(1-2):12-20.
42. Bosmans JC, Geertzen JH, Post WJ, van der Schans CP, Dijkstra PU. Factors associated with phantom limb pain: a 31/2-year prospective study. Clin Rehabil. 2010;24(5):444-453.
43. Borchers AT, Gershwin ME. The clinical relevance of complex regional pain syndrome type I: The Emperor's New Clothes. Autoimmun Rev. 2017;16(1):22-33.
44. Popkirov S, Hoeritzauer I, Colvin L, Carson AJ, Stone J. Complex regional pain syndrome and functional neurological disorders: time for reconciliation. J Neurol Neurosurg Psychiatry. 2018;doi: 10.1136/jnnp-2018-318298.
45. Chang C, McDonnell P, Gershwin ME. Complex regional pain syndrome - False hopes and miscommunications. Autoimmun Rev. 2019;18(3):270-227.

Chapter 8

Decision making process for amputation in case of therapy resistant complex regional pain syndrome type-I in a Dutch specialist Centre

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Med Hypotheses. 2018 Dec;121:15-20

Abstract

Deciding for an amputation in case of complex regional pain syndrome type I (CRPS-I) is controversial. Evidence for favorable or adverse effects of an amputation is weak. We therefore follow a careful and well-structured decision making process. After referral of the patient with the request to amputate the affected limb, it is checked if the diagnosis CRPS-I is correct, duration of complaints is more than 1 year, all treatments described in the Dutch guidelines have been tried and if consequences of an amputation have been well considered by the patient. Thereafter the patient is assessed by a multidisciplinary team (psychologist, physical therapist, anesthesiologist-pain specialist, physiatrist and vascular surgeon). During a multidisciplinary meeting professionals summarize their assessment. Pros and cons of an amputation are discussed, taking into account level of amputation and expectations about post amputation functioning of patient and team. Based on assessments and discussion a consensus based decision is formulated and the patient is informed. If it is decided that an amputation is to be performed, the amputation will follow shortly. If it is decided not to amputate, the decision is extensively explained to the patient.
Incidence of patients suffering from therapy resistant CRPS-I referred for amputation is low and because referred patients are strongly in favor of an amputation, a randomized controlled trial will be difficult to perform. Hence level of evidence in favor or against an amputation will remain low. We therefore report our decision making process to facilitate discussion about this difficult and delicate matter.

Introduction

Amputation in case of longstanding therapy resistant complex regional pain syndrome type-I (CRPS-I) is controversial. In a systematic review outcomes of an amputation in case of longstanding therapy resistant CRPS-I were summarized and discussed (1). That review included 26 case studies and case series (together 107 patients) published between 1948 and 2009. Recurrence of CRPS-I, reported for 61 of the 107 patients, occurred in 31 patients. Fitting of a prosthesis, reported for 49 of 107 patients, resulted in 36 patients receiving a prosthesis but only 14 using it. Satisfaction was reported for 51 of 107 patients but it was unclear if satisfaction referred to pain reduction, increase of functional ability or prevention of infections. That review concluded that, overall outcome reporting was inconsistent and incomplete and given the available evidence, it is not possible to strongly advice against or in favor of amputation in case of longstanding therapy resistant CRPS-I (1).
In a series of clinical papers we reported on amputation of the affected limb in case of longstanding therapy resistant CRPS-I (2-4). The clinical outcomes after amputation for longstanding therapy resistant CRPS-I in our center appeared to be favorable; 95% (20/21) of patients reported improvements in their lives in general, 10 of 15 lower limb amputees (67%) used a prosthesis at least 8 hours per day, 19 patients (90%) reported pain reduction, 17 (81%) reported an increase in mobility and 14 and 12 respectively reported improvements in sleep and mood. Overall 86%

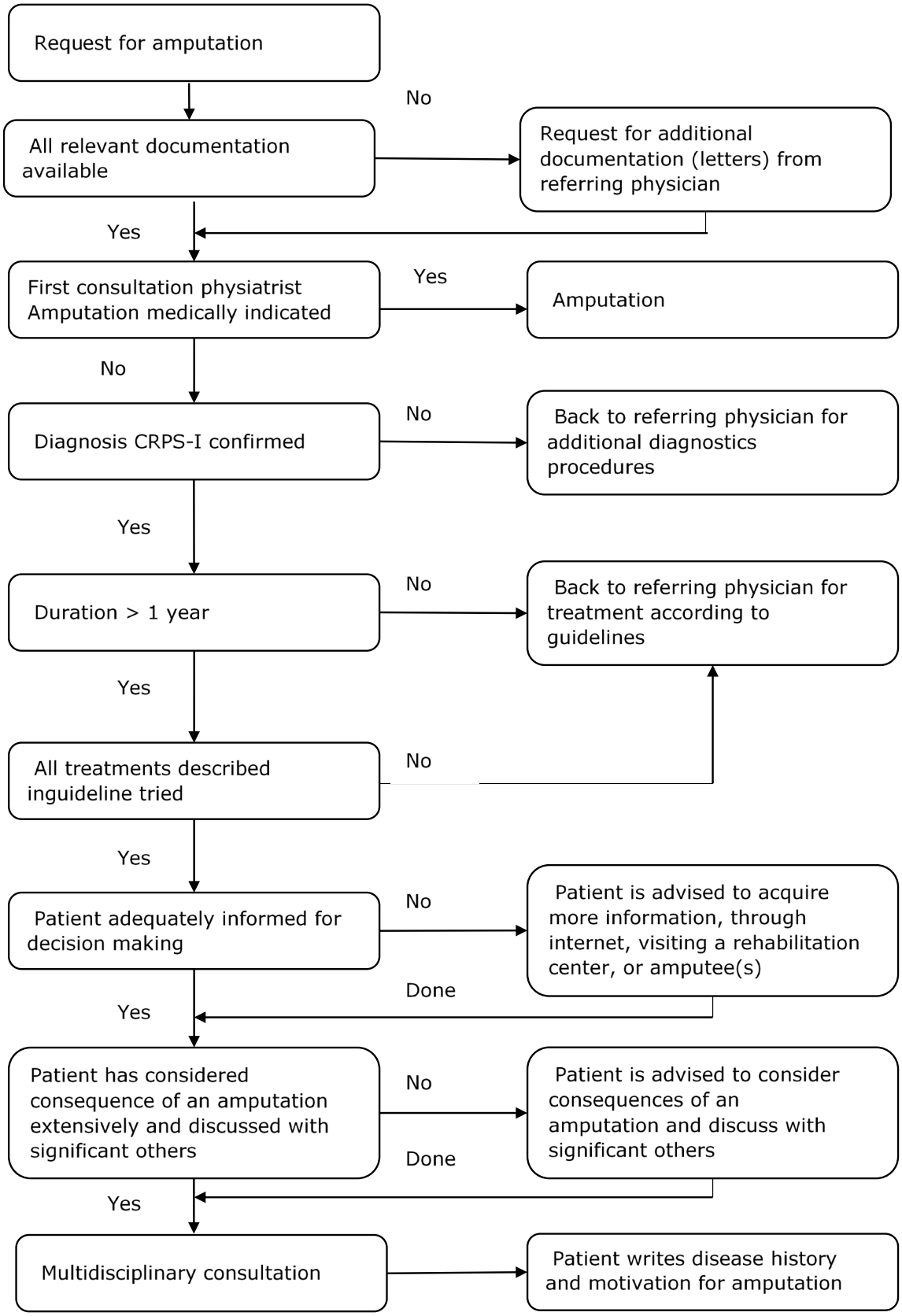
(18/21) patients would choose an amputation again (2). Three amputees even became Paralympic athletes. However, 4 patients experienced deterioration in using the toilet and 6 felt less understood by their peers (2). The research group of Midbari found that patients with CRPS-I who underwent an amputation of the affected limb experience less pain and a better health status assessed by means of the SF36 compared to patients with CRPS-I without an amputation (5). Additionally, CRPS-I patients with an amputation used less medication than those without an amputation (5).
Our series of papers caught attention of patients and professionals and resulted in an increased inflow of requests for an amputation in case of longstanding therapy resistant CRPS-I.
When submitting our manuscripts to journals many reviewers commented on it. Below you will find: "Reviewer comments" published in the PhD thesis of Bodde and *our unpublished thoughts* (6). "I do not think the authors have understood the pathophysiology of CRPS-I". *Who does?* "Amputations for CRPS-I are serious disabling interventions that can be avoided with current treatment strategies". *Which strategies did you have in mind and do you have evidence for your statement?* "It is really astonishing how many amputations were performed during the recruitment period for that study since data tautoo amputation is very scarce in literature". *Didn't you read our systematic review including 26 studies describing 107 patients?* "In the US this surgery is rarely if ever considered an option". *We think we have an alternative if everything else fails!* "The decision to amputate in these cases can be agonizing for surgeon as well as the patient". *At last somebody who understands patients and clinicians, a rare breed*. Interestingly, Midbari and Eisenberg recently reported in a letter to the editor quite similar experiences when submitting their study about amputation and CRPS-I (7).
Within our hospital amputation in case of longstanding therapy resistant CRPS-I was frowned upon and some anesthesiologists refused collaboration to these practices and did not want to provide anesthesia for surgery. Therefore we had to find a dedicated anesthesiologist. Child physicians accused us of mall practice when a child (15 years of age) with longstanding therapy resistant CRPS-I had a trans-tibial amputation. She now is a Paralympic athlete.
The increased inflow of new patients, the limited evidence available, the sometimes disappointing results, the comments of reviewers and responses within our hospital made us re-evaluate the decision making process. Aim of this paper is to present the current status of our decision making process for amputation in longstanding therapy resistant CRPS-I and to stimulate discussion about this topic.

Hypothesis
Deciding for an elective amputation in case of CRPS-1 needs deliberation by an expert team of different specialists and a well-informed patient. Discussion between specialists and weighing all arguments will facilitate the decision making process resulting in an acceptable outcome.

Procedures

Screening before multidisciplinary consultation (Figure 1)
When a patient is referred for assessment of an amputation in case of longstanding therapy resistant CRPS-I the physiatrist needs all correspondence from the referring physician. If this information is not present the information is requested. If all information is present a consultation is planned. During consultation the physiatrist takes the medical history including, education, level of activities, ADL, participation (professionally, as a partner, parent, and recreational, including sports), lifestyle (smoking, alcohol and drugs consumption) and current use of medication. Smoking

Figure 1 Screening before multidisciplinary consultation.



should be assessed and discussed since it increases the risk for reamputation and wound complications in lower limb surgery and lower limb amputations (8-10). Further compliance to secondary preventative measures such as cessation of smoking, a healthy diet, and > 80% compliance to drug prescription reduces cardio-vascular events and mortality after lower limb amputations (11). Regular alcohol consumption is also considered during the decision making process since it is a risk factor for major complications after below knee amputation (12). The physiatrist discusses sexuality, the wish for amputation and tries to exclude Body Integrity Identity Disorder (BIID), auto- mutilation, etc. During physical examination signs for self-induced lesions are looked for since in some patients with CRPS-I these lesions are present and explain part of the symptoms (13). Additionally it is determined whether an amputation is medically necessary for instance in case of life threatening infection or gangrene. If so the vascular surgeon is consulted and an amputation is planned without further multidisciplinary consultation. If an amputation is medically not immediately necessary, the diagnosis CRPS-I is confirmed or refuted based on history, documents and examination following current criteria (Budapest), because in some patients the diagnosis was established a long time ago on diagnostic criteria no longer applicable (14). If the diagnosis CRPS-I is not confirmed the patient is referred back for additional diagnostic procedures and treatment. If the diagnosis is confirmed, it is checked whether duration of symptoms are present for less than 1 year. If so the patient is referred back because within the first year after the diagnosis is made many patients (partly) recover; pain, swelling, range of motion and disability improve (15). If symptoms are present for more than 1 year it is assessed whether all treatments described in Dutch multidisciplinary guidelines have been tried (AppendixS1). These guidelines were developed based on best available evidence.(16). If not the patient is referred back for treatment according these guidelines. If all treatments have been tried without success it is assessed whether the patient is well informed about all possible outcomes of an amputation, positive as well as negative outcomes. If the patient is poorly informed and has not considered thoroughly the impact of an amputation functionally, psychologically and socially, the patient is referred back to acquire further information and further consideration. If the patient is well informed and impact of the amputation has been well considered a multidisciplinary consultation is planned and the patient is asked to write a medical history from a personal perspective and a motivation for the amputation. This expectation is based on general principles of prosthetic rehabilitation and data from our earlier evaluations of patients who received an amputation for a longstanding therapy resistant CRPS-I (2, 3). If patients are better informed prior to amputation they can have more realistic expectations about living with an amputation and if preamputation expectations are met after the amputation patients are more satisfied with outcomes (17).

Multidisciplinary consultation (Figure 2)

During the multidisciplinary consultation the involved professionals are rehabilitation psychologist, physical therapist, anaesthesiologist-pain specialist, vascular surgeon, orthopaedic surgeon (if the patient has an orthopaedic history), and physiatrist. All professionals assess the patient on the same day for reasons of efficiency. The assessment includes psycho-social, physical and medical aspects.

Rehabilitation psychologist

Psychological factors associated with CRPS are pain, depression, anxiety, fear, catastrophizing, stressful life events, resilience and body perception disturbance (15, 18-20). The associations however are not conclusive and are not pointing in a specific direction of a personality disorder or a specific psychopathology (21-24). To assess these factors the patient receives prior to the interview questionnaires at home and is requested to fill them in: for resilience the Connor-Davidson Resilience Scale (CD-RISC), for quality of life the World Health Organization Quality of Life Questionnaire (WHOQOL-BREF), for psychosocial distress the symptom check list (SCL-90-R), for depression the Back depression inventory (BDI-II) and for anxiety the anxiety scale of the hospital

Fig. 1. Flow chart of the decision making process prior to the multidisciplinary consultation for amputation because of CRPS–I anxiety and depression scale (HADS-A)(25-29). Additionally a questionnaire for pain related fear (TAMPA) and pain catastrophizing scale (PCS) is filled in (30, 31). The rehabilitation psychologist assesses in a structured interview the motivation of the patient for an amputation, whether outcome expectations are realistic, and whether the patient is aware of change in body image and of the pros and cons of an amputation. An inventory of finances, housing, work, education, social support, coping, life style, household and activities is made. A screening is performed for cognitive problems and psychiatric disorders such as depression, anxiety, posttraumatic stress syndrome, BIID, auto mutilation and conversion disorders. The psychologist assesses lawsuits, currently or in the past, treatment for any mental problem, addiction, and outstanding or disrupting life events or adversity (for instance severe disease of death of a significant other, physical, mental or sexual abuse, molest, etc.). The results of the questionnaires together with the written motivation of the patient is discussed and used to assess the process of decision making of the patient. Was the decision discussed with significant others and friends, are outcome expectations realistic, is there a goal to achieve and how is the awareness of the complications? During this interview it is also assessed, if the patient is well prepared for an amputation, and resilient enough. What were patients reactions in the past on adversity? Are the circumstances (financial, housing, social support, life style, cognition) satisfactory? Is the CRPS connected to a lawsuit or a mental illness (BIID, auto-mutilation)?

Physical therapist

The physical therapist assesses body mass index (BMI), core stability, one leg balance, range of motion of hips and knees, muscle strength of large muscle groups of arms and legs, use of walking aids and independence of transfers. If the patient wishes an amputation but does not wish to walk with a prosthesis the assessment is limited to BMI, core stability, and one leg balance test. Although BMI is not a predictor for walking ability following lower limb amputation it should be taken into account in the decision making process (32, 33). A high BMI has shown to be a risk factor for wound complications and poorer survival in lower limb amputations (8, 34). Additionally weight is taken into account because a larger weight and a larger waist circumference is associated with less distance on the 6 minute walking test (35). An overly low BMI (< 15), is also considered since it is a risk factor for post amputation mortality in below knee amputation for critical ischemia limbs (8, 35). Results of the one leg balance test are compared to the

normative values found previously (36). One leg balance is predictor for success in prosthetic ambulation and prosthetic use (33). A too high or too low BMI may be relative contra indications for an amputation. Sometimes a too low BMI is the result of longstanding inactivity and patients do not have enough muscles and supporting tissue to wear a prosthesis. An amputation may, however, be considered when after a dietary intervention combined with exercises BMI has increased up to 18 in case of a low BMI and muscle strength is adequate after physical therapy. In case of a too high BMI, an amputation is considered if BMI has been reduced to below 25. Also a relative contra-indication for an amputation is the lack of muscle control proximal to the proposed level of amputation or insufficient muscle control of arms or trunk. If after a training program muscle control is adequate an amputation can be performed.

Anesthesiologist-pain specialist

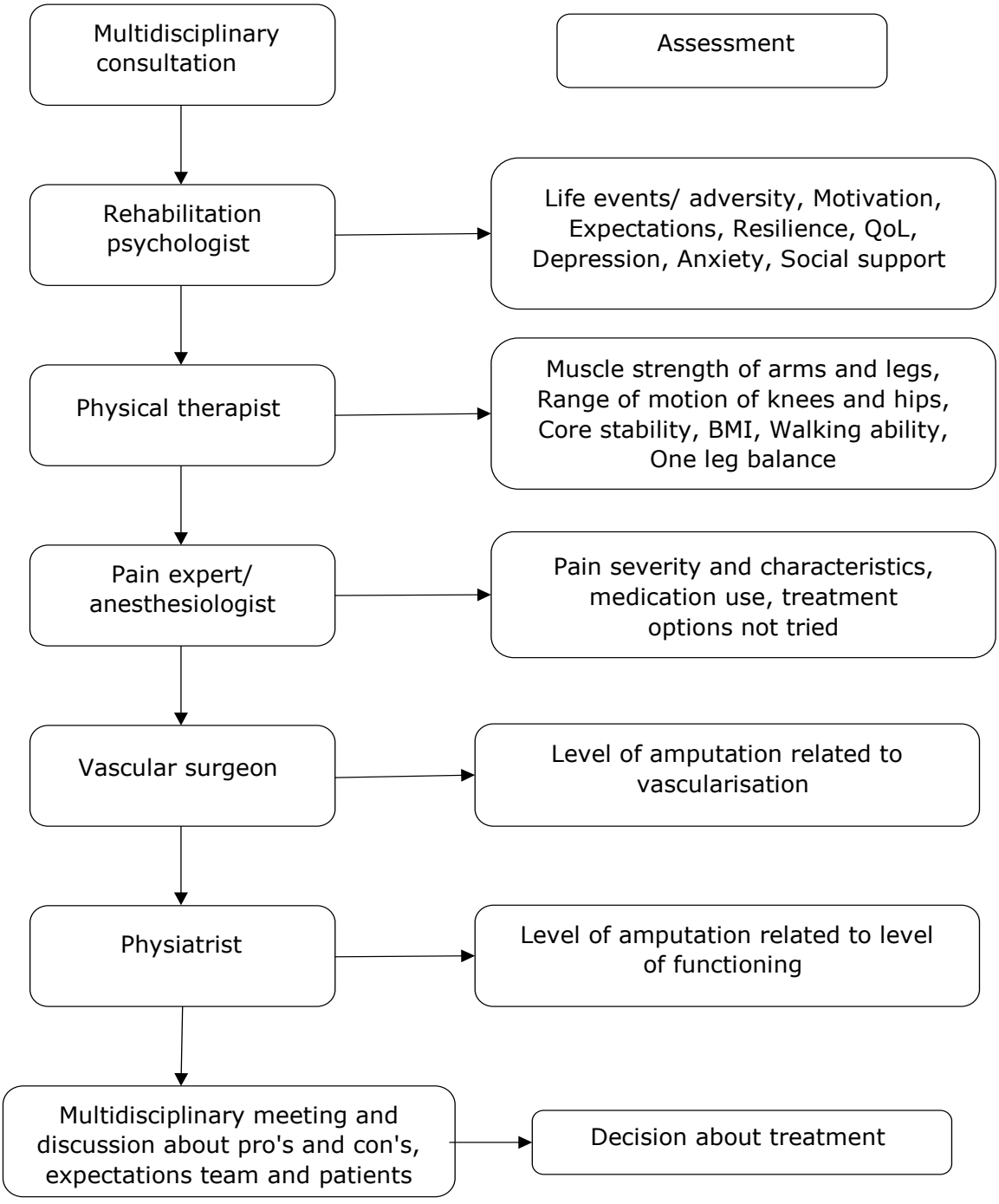
The anesthesiologist-pain specialist assesses pain nature, severity and characteristics, sensory disturbances, to confirm CRPS-I and to exclude other pain problems. Further impact of pain is assessed, as well as medication use and previous treatments. Special attention is paid to the patient having had reasonably all pain treatments including invasive interventions in an adequate way, according to the (revised) Dutch Guideline Type 1 Complex Regional Pain Syndrome (16). The anesthesiologist discusses the patients expectations with respect to pain and functional gain in case an amputation will be executed. He informs the patient if expectations are not realistic. The post-operative phantom pain and stump pain incidence and potential CRPS-recurrence are brought up to help the patient consider pros and cons. If the patients' general condition gives rise to increased surgery related anesthesiological risks, the anesthesiologist discusses these also.

Vascular surgeon and physiatrist

The vascular surgeon and the physiatrist see the patient together. They again ask the patient to explain the wish for an amputation and perform a physical examination aimed at macroscopic appearance of the leg in terms of deformity and discrete signs of CRPS-I, including the most proximal level of these signs and symptoms. Pulses are verified at the levels of common femoral, popliteal, dorsal pedal and posterior tibial arteries. Other signs of diminished vascularization are checked as well, by e.g. capillary refill. When, after physical examination, there is suspicion of peripheral artery occlusive disease, additional duplex ultrasound is planned. When hemodynamically significant stenoses are found in the iliaco-femoro-popliteal tract additional contrast enhanced computerized tomography scanning is performed and subsequent invasive treatment is considered. Treatment may include PTA/stenting or bypass surgery and reasons for treatment may include the relief of symptoms accompanying symptoms caused by CRPS-1 or to assure an appropriate wound healing after amputation.

Both vascular surgeon and physiatrist then propose the level of amputation. To prevent recurrence of CRPS level of amputation is chosen proximal of the area of allodynia (only based on clinical experience). Additionally functionality after the amputation is taken into account when deciding level of amputation. If the patient does not want to walk after the amputation the proposed level is based on optimal wheelchair mobility or on optimal nursing care. If the patient wants to walk after the amputation the proposed level is based on optimal functionality with a prosthesis. Further they re-evaluate the medication and discuss the pros and cons of an amputation. Also the risks and possible complications of an amputation are discussed. The rehabilitation process is explained.

Fig 2 Flow chart of the multidisciplinary consultations and assessment for amputation because of CRPS -I



Multidisciplinary meeting
During the multidisciplinary meeting each professional summarizes his/her assessment and reports his/her opinion about the pros and cons of an amputation for this particular patient, the level of amputation and the expectations of the level of functioning after an amputation. These assessments are compared with wishes and expectations of the patient described in the letter of motivation. Based on the acquired information and discussion, a consensus based decision is formulated and the patient is informed by the physiatrist and the surgeon on the same day about the decision. If it is decided that an amputation is to be performed the patient is put on a waiting list for the procedure and generally an amputation is performed within two months after the multidisciplinary meeting. If no amputation is advised reasons will be extensively explained to the patient. Depending on the outcomes of the multidisciplinary meeting, further diagnostics and or additional (pain) treatments may be proposed. The referring physician is informed about the outcomes of the multidisciplinary consultations and the decision.

Considerations

Patients suffering from longstanding therapy resistant CRPS-I generally request an amputation because of severe spontaneous pain often including allodynia, not controllable by means of treatment (medication, invasive pain procedures or other treatments according to the guidelines (16). Pain prevents them in performing activities of daily life and personal care and participating in society (recreationally, professionally, as a partner or parent). The affected limb is often completely a-functional and referred to as "that leg" instead of "my leg". The affected limb is no longer included in their body scheme. Patients cannot stand the pain anymore and want to become active again and want to participate in society. They want to "get rid of that limb".
Patients are referred to the department of Rehabilitation Medicine of the University Medical Center Groningen (UMCG) for amputation because relevant health care professionals elsewhere in the Netherlands are not amenable for amputation requests or miss expertise. Since 2000 amputations for this reason are performed in our center and due to ongoing research an expert center emerged.
Amputation of a limb is an irreversible and drastic measure, and it may have large consequences, negative as well as positive, for person and peers involved. CRPS-I may not be solved by an amputation, it may reoccur more proximally in the stump or in another extremity (1). Because CRPS-I is associated with central nervous system alterations (37, 38) an amputation may not result in the expected / desired pain reduction or functional gain. However, despite central nervous system alterations our amputation results were quite favorable. A reduction in pain following amputation was reported by 19 patients and for 18 of them it was a major reduction. But 18 patients reported residual limb pain and 18 experienced phantom limb pain which impeded them much to very much in 6 respectively 7 patients. Despite residual limb pain and phantom pain 18 out of 21 patients would chose an amputation again (2). However, recently, a case-report documented a patient who had undergone an amputation because of CRPS-I but who now advocates against amputation (39).

Taking the above in to account the decision to amputate in case of longstanding therapy resistant CRPS-I is difficult. By weighing all pros and cons carefully by professionals and patient in an expert center the chance of making decision which is beneficial for the patient is increased. Overlap in topics of assessments of the professionals involved exists to be sure that consistent information is acquired during the whole decision making procedure.
Reasons not to amputate are psychiatric disorders such as BIID, conversion or auto-mutilation, addiction of the patient to medication, alcohol or drugs, a previous amputation because of CRPS-I, patient expectations are unrealistically high, professionals do not expect functional or quality of life improvement due to an amputation. After the discussion the patient is informed. Most referred patients themselves already decided that they wanted an amputation. Their decision is more or less made independently from peers or health care professionals (17). If the decision of the team differs (no amputation) from what they want (amputation), the decision is extensively discussed and explained. Sometimes patients are (very) disappointed and they visit another hospital to request for an amputation.
Overall level of evidence for effects of treatments of CRPS-I is low. Level of evidence for effects of amputation in case of therapy resistant CRPS-I is even lower. Additionally, because patients referred for amputation are strongly motivated to undergo that amputation it is difficult to a randomized controlled trial. Hence level of evidence in favor or against an amputation will remain low. Predicting poor or successful outcomes after amputation in case of therapy resistant CRPS-I accurately, is currently not possible.
We described and presented the multidisciplinary decision making process as prevailing in our university center in detail, with respect to amputation in therapy resistant CRPS-I patients. Our experience is based on a period of 24 years with patients that are referred from whole the country (the Netherlands). In this way we hope to contribute into an open discussion about this difficult and delicate matter.

References

1. Bodde MI, Dijkstra PU, den Dunnen WF, Geertzen JH. Therapy-resistant complex regional pain syndrome type I: to amputate or not? J Bone Joint Surg Am 2011;93:1799-1805.
2. Krans-Schreuder HK, Bodde MI, Schrier E, et al. Amputation for long-standing, therapy-resistant type-I complex regional pain syndrome. J Bone Joint Surg Am 2012;94:2263-2268.
3. Bodde MI, Dijkstra PU, Schrier E, van den Dungen JJ, den Dunnen WF, Geertzen JH. Informed Decision-Making Regarding Amputation for Complex Regional Pain Syndrome Type I. J Bone Joint Surg Am 2014;96:930-934.
4. Bodde MI, Schrier E, Krans HK, Geertzen JH, Dijkstra PU. Resilience in patients with amputation because of Complex Regional Pain Syndrome type I. Disabil Rehabil 2014;36:838-843.
5. Midbari A, Suzan E, Adler T, et al. Amputation in patients with complex regional pain syndrome: a comparative study between amputees and non-amputees with intractable disease. Bone Joint J 2016;98-B:548-554.

6. Bodde, M. I. (2014). Complex Regional Pain Syndrome type I and Amputation. Groningen: s.n.
7. Midbari A, Eisenberg E. Is the Pain Medicine Community Reluctant to Discuss Limb Amputation in Patients with Intractable Complex Regional Pain Syndrome? Pain Med 2017;18:1406-1407.
8. Hasanadka R, McLafferty RB, Moore CJ, Hood DB, Ramsey DE, Hodgson KJ. Predictors of wound complications following major amputation for critical limb ischemia. J Vasc Surg 2011;54:1374-1382.
9. Acar E, Kacira BK. Predictors of Lower Extremity Amputation and Reamputation Associated With the Diabetic Foot. J Foot Ankle Surg 2017;56:1218-1222.
10. Kim JH, Patel S. Is It Worth Discriminating Against Patients Who Smoke? A Systematic Literature Review on the Effects of Tobacco Use in Foot and Ankle Surgery. J Foot Ankle Surg 2017;56:594-599.
11. Shalaeva EV, Saner H, Janabaev BB, Shalaeva AV. Tenfold risk increase of major cardiovascular events after high limb amputation with non-compliance for secondary prevention measures. Eur J Prev Cardiol 2017;24:708-716.
12. Belmont PJ,Jr, Davey S, Orr JD, Ochoa LM, Bader JO, Schoenfeld AJ. Risk factors for 30-day postoperative complications and mortality after below-knee amputation: a study of 2,911 patients from the national surgical quality improvement program. J Am Coll Surg 2011;213:370-378.
13. Mailis-Gagnon A, Nicholson K, Blumberger D, Zurowski M. Characteristics and period prevalence of self-induced disorder in patients referred to a pain clinic with the diagnosis of complex regional pain syndrome. Clin J Pain 2008;24:176-185.
14. Harden RN, Bruehl SP. Diagnosis of complex regional pain syndrome: signs, symptoms, and new empirically derived diagnostic criteria. Clin J Pain 2006;22:415-419.
15. Bean DJ, Johnson MH, Heiss-Dunlop W, Kydd RR. Extent of recovery in the first 12 months of complex regional pain syndrome type-1: A prospective study. Eur J Pain 2016;20:884-894.
16. Perez RSGM, Geertzen JHB, Dijkstra PU, et al. Revised guidelines Complex Regional Pain Syndrome Type 1 Richtlijn herziening Complex Regionaal Pijn Syndroom Type-I). 2014;2017:199.
17. Quon DL, Dudek NL, Marks M, Boutet M, Varpio L. A qualitative study of factors influencing the decision to have an elective amputation. J Bone Joint Surg Am 2011;93:2087-2092.
18. Geertzen JH, de Bruijn-Kofman AT, de Bruijn HP, van de Wiel HB, Dijkstra PU. Stressful life events and psychological dysfunction in Complex Regional Pain Syndrome type I. Clin J Pain 1998;14:143-147.
19. Bruehl S, Husfeldt B, Lubenow TR, Nath H, Ivankovich AD. Psychological differences between reflex sympathetic dystrophy and non-RSD chronic pain patients. Pain 1996;67:107-114.
20. Bean DJ, Johnson MH, Heiss-Dunlop W, Lee AC, Kydd RR. Do psychological factors influence recovery from complex regional pain syndrome type 1? A prospective study. Pain 2015;156:2310-2318.

21. Puchalski P, Zyluk A. Complex regional pain syndrome type 1 after fractures of the distal radius: a prospective study of the role of psychological factors. J Hand Surg Br 2005;30:574-580.
22. de Mos M, Sturkenboom MC, Huygen FJ. Current understandings on complex regional pain syndrome. Pain Pract 2009;9:86-99.
23. Beerthuizen A, Stronks DL, Huygen FJ, Passchier J, Klein J, Spijker AV. The association between psychological factors and the development of complex regional pain syndrome type 1 CRPS1)--a prospective multicenter study. Eur J Pain 2011;15:971-975.
24. Lohnberg JA, Altmaier EM. A review of psychosocial factors in complex regional pain syndrome. J Clin Psychol Med Settings 2013;20:247-254.
25. Spinhoven P, Ormel J, Sloekers PP, Kempen GI, Speckens AE, Van Hemert AM. A validation study of the Hospital Anxiety and Depression Scale HADS) in different groups of Dutch subjects. Psychol Med 1997;27:363-370.
26. Arnau RC, Meagher MW, Norris MP, Bramson R. Psychometric evaluation of the Beck Depression Inventory-II with primary care medical patients. Health Psychol 2001;20:112-119.
27. Arrindell WA, Ettema JHM. Symptomchecklist Handleiding bij een multidimensionele psychopathologie-indicator Symptom Checklist, Manual for a multidimensional psychopathology indicator). Lisse: Swets Test Publishers; 2003.
28. Connor KM, Davidson JR. Development of a new resilience scale: the Connor-Davidson Resilience Scale (CD-RISC). Depress Anxiety 2003;18:76-82.
29. Skevington SM, Lotfy M, O'Connell KA, WHOQOL Group. The World Health Organization's WHOQOL-BREF quality of life assessment: psychometric properties and results of the international field trial. A report from the WHOQOL group. Qual Life Res 2004;13:299-310.
30. Vlaeyen JW, Kole-Snijders AM, Boeren RG, van Eek H. Fear of movement/(re)injury in chronic low back pain and its relation to behavioral performance. Pain 1995;62:363-372.
31. Roelofs J, van Breukelen G, Sluiter J, et al. Norming of the Tampa Scale for Kinesiophobia across pain diagnoses and various countries. Pain 2011;152:1090-1095.
32. Sansam K, Neumann V, O'Connor R, Bhakta B. Predicting walking ability following lower limb amputation: a systematic review of the literature. J Rehabil Med 2009;41:593-603.
33. Kahle JT, Highsmith MJ, Schaepper H, Johannesson A, Orendurff MS, Kaufman K. Predicting Walking Ability Following Lower Limb Amputation: an Updated Systematic Literature Review. Technol Innov 2016;18:125-137.
34. Lin CW, Hsu BR, Tsai JS, et al. Effect of limb preservation status and body mass index on the survival of patients with limb-threatening diabetic foot ulcers. J Diabetes Complications 2017;31:180-185.
35. Linberg AA, Roach KE, Campbell SM, et al. Comparison of 6-minute walk test performance between male Active Duty soldiers and servicemembers with and without traumatic lower-limb loss. J Rehabil Res Dev 2013;50:931-940.
36. Springer BA, Marin R, Cyhan T, Roberts H, Gill NW. Normative values for the unipedal stance test with eyes open and closed. J Geriatr Phys Ther 2007;30:8-15.

37. Carcamo CR. Bimodal Modulation of Ipsilateral Spinal-Coeruleo-Spinal Pathway in CRPS: A Novel Model for Explaining Different Clinical Features of the Syndrome. Pain Med 2015;16:1589-1596.
38. Hotta J, Zhou G, Harno H, Forss N, Hari R. Complex regional pain syndrome: The matter of white matter? Brain Behav 2017;7:e00647.
39. Goebel A, Lewis S, Phillip R, Sharma M. Dorsal Root Ganglion Stimulation for Complex Regional Pain Syndrome (CRPS) Recurrence after Amputation for CRPS, and Failure of Conventional Spinal Cord Stimulation. Pain Pract 2018;18:104-108.

Chapter 9

General discussion

Background

The aim of this thesis was to explore psychological aspects in rehabilitation. In the introduction Engel's biopsychosocial model was presented (*chapter 1*). This model adds psychological and social influences to the biomedical model and gives room for the fact that body and brain influence each other. But integration of that model in medical research seems hard since research into effects of psychological interventions in medical research is scarce. As a psychologist it was frustrating to realize that in general psychological influences on restrictions or other consequences of diseases or trauma were hardly studied, nevertheless it motivated me to find answers on the questions posed in the introduction.

Chapters

-QOL study-
Rehabilitation outpatients scored lower on all World Health Organisation Quality Of Life-abbreviated version (WHOQOL-bref) domains compared to Dutch population, thereby confirming the model of Engel [1] (*chapter 2*) but the differences on the psychological and social domain were small. The impact of chronic pain on Quality of Life (QOL) in patients was found to be higher compared to patients with musculoskeletal problems. For these two patient groups outcomes can be used as norm scores. The advantage of the WHOQOL-bref is that it provides a comprehensive overview of the adaption of the patient to their disease or trauma because all domains are assessed.
-Cognitive dysfunction study-
Rehabilitation patients, without brain damage, had higher scores on the Cognitive Failure Questionnaire compared to the Dutch population (*chapter 3*). High stress coping ability (resilience) was protecting against cognitive failure, while there was a mediating effect of anxiety and depression. The hypothesised association between cognition and surgery or pain, found in other studies, was not confirmed in our study.[2,3]
-Prosthesis satisfaction review-
The systematic review into prosthesis satisfaction (*chapter 4*) showed that satisfaction with a prosthesis was associated with many factors which could be grouped in 5 domains i.e. appearance, properties, fit, and use of the prosthesis, as well as aspects of the residual limb. Significance of the associations was related to gender, liner use, etiology and level of amputation. However, questionnaires assessing satisfaction use different operationalization's of satisfaction. In addition without providing a clear definition of satisfaction in the user guides, comparisons between study results are difficult.
-Resilience in CRPS-I study-
The mean resilience scores and mean scores on all domains of the WHOQOL-bref of patients who were amputated because of longstanding therapy resistant CRPS-I were higher than those patients with chronic pain (*chapter 5*). These results suggest that patients with resilience are capable of adapting to their new (post amputation) situation and improving their QOL.

-Association with outcome study-
Poor social support or lower score on resilience were associated with poor outcomes of an amputation in case of longstanding therapy resistant CRPS-I (*chapter 6*). These finding were somewhat disappointing because we expected associations with more psychological factors. The factors found to be associated with the outcome seem to be general factors, not specific for longstanding therapy resistant CRPS-I.
-Outcome study-
More than 75% of patients who were amputated because of longstanding therapy resistant CRPS-I reported an improvement in mobility and or a reduction in pain (*chapter 7*). Recurrence of CRPS-I occurred in the residual limb of 1 participant and in another limb of 3 participants. Despite these good result most patients still had pain and problems with their mobility. The outcomes were stable over time. These outcomes enable us to inform patients who consider an amputation for longstanding therapy resistant CRPS-I.
-Decision paper-
Because amputation in case of longstanding therapy resistant CPRS-I is controversial we described the decision making process in detail (*chapter 8*). We aimed to be transparent for patients and professionals. It forced us to reflect critically upon the decision making process and give others an opportunity to engage in a discussion about this process.

General reflection

Before the case, presented in the introduction, is discussed again in the light of our findings I will start with some more general assumptions. The result of the QOL study showed, that all domains of QOL are affected by physical problems, showing that the biomedical model is too restricted. This is in no way a new insight, it is only a confirmation of what was suggested more than 40 years ago by Engel. He noticed that the physician-patient relationship was deteriorating despite medical technical developments and innovations. The human side of illness and patient care had not developed. Additionally knowledge about the human behaviour had not been integrated: a missed chance to a more effective patient care and health maintenance.[4] Also, in the biomedical model is no room for the fact that patients want to be heard, understood and respected, and want to be involved in decision making.[5-7] These needs of patients is a development of the last decades, encouraged by health care providers.[8]
The restrictions of the biomedical model are based on Christian orthodoxy, leaving the connection with the soul, morale, mind and behavior out of this model.[4]
Nowadays we are aware of different body-brain connections in the human body e.g.: the hypothalamic-pituitary-adrenal axis, the autonomic nervous system, the immune system and the gut-brain axis,[9-13] that confirm the connection between body and brain.
This thesis is predominantly about psychological aspects of rehabilitation. It may seem that it undermines the idea of everything being interconnected by focusing on one domain. We had to select and sometimes the focus became narrow and for that

reason other aspects were ignored. In the cognitive dysfunction study for instance, we did not investigate the physical (dys)function.
In the prosthesis satisfaction review (*chapter 4*) a wide search strategy was applied to find studies investigating not only psychological domain but also the physical and the social domain. However with that broad search strategy other difficulties surfaced. A lot of different factors were associated with prosthesis satisfaction, despite the restriction of including only patients with a trans-tibial amputation. Comparison of the importance of the different factors was almost impossible due to different outcome measures (questionnaires) and study designs. In the end we just summarized all factors to get a grasp.
Another difficulty in the prosthesis satisfaction review was how factors were operationalized. Different questionnaires applied different operationalizations which were poorly documented. Some questionnaires did not have a user guide making it even more difficult to interpret results of the different questionnaires.
The last four chapters are about patients with longstanding therapy resistant CRPS-I. We encountered other difficulties in those studies. The first one was the definition of CRPS-I, which has changed a few times over the last 15 years.[14] Those changes are highly relevant when including patients in studies, determining prevalence, determining recurrence rate and when comparing outcomes of different studies.[15] But even the latest definition is under scrutiny. Some critics even state that it is not a disease at all or report overlap with other diseases and that the validity of the criteria is not sufficient and not tested thoroughly.[16,17]
A second difficulty is: how long is the diagnosis of CRPS-I valid? Most diseases have a dynamic character which is not often taken into account. For instance a person fractured a leg, becomes depressed and 10 years later developed CRPS-I which proved to be therapy resistant CRPS-I. When assessing the patient for an amputation the fracture has healed and the depression has resolved. Should we consider one of those as a factor potentially influencing the outcome of the amputation? Is the fact that the leg has fractured a sign of vulnerability? Or is the fact that the fracture has healed a sign of strength? For depression the same considerations can be made. Is depression a sign of vulnerability? Or is the fact that the patient left the depression behind a sign of strength? In general when documenting a patient's history all diagnoses are summarized but not if and how they were handled, and how the patient coped with those diagnoses. What is the value of the diagnoses 10 years after the event? I have no answers to these questions although I personally think that most of the time the way a patient handles adversity is telling me more than what kind of adversity it actually was.
The third difficulty is the goal of an amputation and interpretation of the outcome. There may be different goals a patients aims for when requesting an amputation e.g. decrease in pain, increase in mobility and or decrease infection risk. It is challenging to weigh these different goals. Is one goal more important than the other and what if a participant achieves only one of the three goals, can it be rated as an improvement or not? And if one goal is only reached for 33%, for example the pain (on a 0-10 scale) decreased from 9 to 6, how should it be rated? In my opinion even the partial realization of a goal, especially if the result improve function or QOL, is a positive

outcome. For example the decrease in pain counteracts insomnia and provides a better QOL.[18]
The fourth difficulty is a possible selection bias in our studies. Many patients with CRPS-I experience a decrease of the symptoms within 6-13 months after the onset.[19] A small group of patients progress to a longstanding therapy resistant CRPS-I. The CRPS-I patients in our studies have longstanding therapy resistant CRPS-I and differ from the other CRPS-I patients, seen by the family physician with regard to age and location of the CPRS-I.[20] The participants in the outcome study are younger and the lower limb is mostly affected. Actually our participants have more in common with samples in other studies with longstanding therapy resistant CRPS-I.[21] Younger participants and more lower limb amputations could both influence the outcome in a positive way. Younger people have more rehabilitation possibilities and the use of a lower limb prosthesis is more straightforward compared to the use of upper limb prosthesis.
Despite these difficulties the studies revealed new insights. For me it was surprising that childhood adversity and disturbing life events were not associated with a poor outcome. The relationship between adverse childhood experiences and poorer health across the life course is well established.[22-24] Additionally early adversity predisposes to chronic pain.[25] Further childhood adversity can affect the brain itself, reducing stress coping mechanism.[26,27] In CRPS-I patients stressful life events are more common, suggesting that it could be a risk factor for CRPS-I.[28] But is stress or childhood adversity influencing the outcome of an amputation in case of longstanding therapy resistant CRPS-I? We did not find such an association in the outcome study. It is possible that adversity is boosting resilience reducing the effects of adversity on outcome. Mechanism and model behind this possibility have repeatedly been investigated.[29-31] Resilience research started after the realization that childhood adversity was handled by many children in a sufficient way and the researchers wondered why.[32,33] They named the competence to handle childhood adversity: resilience. Later questionnaires were developed to measure resilience. We used the Conner Davidson resilience scale (CD-RISC) developed in 2003.[34] This questionnaire is based on different sources, for example Kobasa's work with the construct of hardiness.[35] A last remark about resilience is that although it can grow under influence of adversity the growth is not unlimited.[36]
All the difficulties and ideas concerning patients with longstanding therapy resistant CRPS-I come together in the decision making process "to amputate or not" and led to the studies of this thesis. Another way to handle as a researcher the amputation dilemma is to describe the procedure in detail and share it with others and invite them to a discussion. The process of describing the procedure forces team members to think critically about the rationale behind each step. It necessitates discussion between team members and because the team is multidisciplinary a wide view is required.
Strength and weaknesses:
The QOL study was performed in a consecutive sample of more than 500 patients and only 11% of those was excluded, making the outcomes robust. The sampling was performed in only one facility and all patients had been referred to the psychologist, reducing external validity. In the cognition study different factors were

explored in a regression model in a consecutive sample of 274 patients. However the study was limited because only one (subjective) instrument was used to measure cognition.
The outcome study included 48 participants with an amputation because of longstanding therapy resistant CRPS-I. Although the absolute sample size was small it is one of the larger samples regarding this group described in literature and part of the participants (n=17) participate in a follow up study. Limitation of that study was the lack of a control, group. However norm data found in chapter 2 helped with the interpretation of the outcomes.

Back to the case presented in the introduction of this thesis.(page 11)
Can the results of this thesis be applied in daily practice.
"Is the proposed amputation for this CRPS-I patient, a 45 year old man, the right decision?" was one of the referrals 15 years ago. At the time my mind just wondered in many different directions, not noticing that a vital part of the question was missing. The right decision for what? Are we talking about outcome? And is that the outcome the physician has in mind or the outcome the patient is aiming for? Within rehabilitation the International Classification of Functioning, Disability and Health (ICF), is used 37. The ICF model measures on 3 different levels: body structure and function e.g. edema, pain, muscle weakness; activity e.g. standing, transfers; participation e.g. work, sports. Which level are we talking about and is one of those levels more important than the other? In the outcome study different outcomes were assessed but in daily practice of the decision making process two outcomes are currently considered crucial i.e. decrease of pain and increase in mobility. Associated with these two crucial outcomes are social support and resilience. Patients who experience strong social support and who are resilient have a better chance on a good outcome after the amputation. Although the results were statistically significant in the "Association with outcome study" the model was not perfect.
Another way of looking at the referral of the rehabilitation physician is to evaluate the thinking process of the patients. Is the patient able to think clearly? Beside the cognitive side of thinking, the thinking process was discussed in the team and two crucial factors were acknowledged. Has the patient weighed the consequences of an amputation (pro and con's) thoroughly and has the patient discussed an amputation it with family or close friends? The last step in the decision making process is to compare outcome expectations of team and patient. The team discusses expectations and then compares it with the those of the patient. If the patient has a much more optimistic outcome expectation compared with that of the team, the request for an amputation is turned down.
Conclusion is that currently, if we have to decide if an amputation might be a treatment for the patient, a decision protocol is available and gives me the tools to make a decision from the psychological point of view.

Future research
The results presented in this research are a small step forward, but future research regarding the following topics is needed.
In order to improve the explained variation, presented in the association with outcome study, other psychological factors such as fear of movement, that were identified in other recent studies should be further explored.[38]
In evaluating long term outcome fixed evaluation times should be applied, for instance a measurement at 1, 2 and 5 years after amputation.
Patients who wanted an amputation but the team decided against it should be included in a follow-up study to explore outcomes in this group of patients.

General conclusions

Resilience, cognition, social support, anxiety, depression and pain are associated with outcome (QOL) of rehabilitation outpatients. Integration of psychology in (rehabilitation) medicine will not only enrich the diagnostic opportunities but also increase the therapeutic options. The dare of Engel of 40 years ago is still the same, all medical specialists increase their skills but quality of collaborations has not increased. Hence we all need to widen our view.

References

1. De Vries, J., & Den Oudsten, B. L. Handleiding WHOQOL-100 en WHOQOL-BREF. Herziene versie [manual WHOQOL-100 and WHOQOL-BREF. Revised version]. Tilburg: Tilburg, 2015.
2. Wu CL, Hsu W, Richman JM, et al. Postoperative cognitive function as an outcome of regional anesthesia and analgesia. Reg Anesth Pain Med 2004; 29: 257-268.
3. Rudolph JL, Schreiber KA, Culley DJ, et al. Measurement of post-operative cognitive dysfunction after cardiac surgery: a systematic review. Acta Anaesthesiol Scand 2010; 54: 663-677.
4. Engel GL. The biopsychosocial model and the education of health professionals. Ann N Y Acad Sci 1978; 310: 169-187.
5. Bunn F, Goodman C, Russell B, et al. Supporting shared decision making for older people with multiple health and social care needs: a realist synthesis. BMC Geriatr 2018; 18: 165-018-0853-9.
6. Wampold BE. How important are the common factors in psychotherapy? An update. World Psychiatry 2015; 14: 270-277.
7. Engel GL. The need for a new medical model: a challenge for biomedicine. Science 1977; 196: 129-136.
8. Anonymous 3goede vragen, https://3goedevragen.nl/ (2019).
9. Sandstrom A, Peterson J, Sandstrom E, et al. Cognitive deficits in relation to personality type and hypothalamic-pituitary-adrenal (HPA) axis dysfunction in women with stress-related exhaustion. Scand J Psychol 2011; 52: 71-82.

10. Kennedy PJ, Clarke G, Quigley EMM, et al. Gut memories: Towards a cognitive neurobiology of irritable bowel syndrome. Neurosci Biobehav Rev 2012; 36: 310-340.
11. Hennig-Fast K, Werner NS, Lermer R, et al. After facing traumatic stress: brain activation, cognition and stress coping in policemen. J Psychiatr Res 2009; 43: 1146-1155.
12. Sarzi-Puttini P, Atzeni F and Mease PJ. Chronic widespread pain: from peripheral to central evolution. Best Pract Res Clin Rheumatol 2011; 25: 133-139.
13. Dinan TG and Cryan JF. The Microbiome-Gut-Brain Axis in Health and Disease. Gastroenterol Clin North Am 2017; 46: 77-89.
14. Iolascon G, de Sire A, Moretti A, et al. Complex regional pain syndrome (CRPS) type I: historical perspective and critical issues. Clin Cases Miner Bone Metab 2015; 12: 4-10.
15. Perez RS, Zollinger PE, Dijkstra PU, et al. Evidence based guidelines for complex regional pain syndrome type 1. BMC Neurol 2010; 10: 20-2377-10-20.
16. Popkirov S, Hoeritzauer I, Colvin L, et al. Complex regional pain syndrome and functional neurological disorders: time for reconciliation. J Neurol Neurosurg Psychiatry 2018; doi: 10.1136/jnnp-2018-318298.
17. Chang C, McDonnell P and Gershwin ME. Complex regional pain syndrome - False hopes and miscommunications. Autoimmun Rev 2019;18(3):270-278.
18. Campbell P, Tang N, McBeth J, et al. The role of sleep problems in the development of depression in those with persistent pain: a prospective cohort study. Sleep 2013; 36: 1693-1698.
19. Bean DJ, Johnson MH and Kydd RR. The outcome of complex regional pain syndrome type 1: a systematic review. J Pain 2014; 15: 677-690.
20. de Mos M, de Bruijn AG, Huygen FJ, et al. The incidence of complex regional pain syndrome: a population-based study. Pain 2007; 129: 12-20.
21. Bodde MI, Dijkstra PU, den Dunnen WF, et al. Therapy-resistant complex regional pain syndrome type I: to amputate or not?. J Bone Joint Surg Am 2011; 93: 1799-1805.
22. Jones GT. Psychosocial Vulnerability and Early Life Adversity as Risk Factors for Central Sensitivity Syndromes. Curr Rheumatol Rev 2016; 12: 140-153.
23. Chen M and Lacey RE. Adverse childhood experiences and adult inflammation: Findings from the 1958 British birth cohort. Brain Behav Immun 2018; 69: 582-590.
24. Alvarez HAO, Kubzansky LD, Carnpen MJ, et al. Early life stress, air pollution, inflammation, and disease: An integrative review and immunologic model of social-environmental adversity and lifespan health. Neurosci Biobehav Rev 2018; 92: 226-242.
25. Lane RD, Anderson FS and Smith R. Biased Competition Favoring Physical Over Emotional Pain: A Possible Explanation for the Link Between Early Adversity and Chronic Pain. Psychosom Med 2018; 80: 880-890.
26. Burke NN, Finn DP, McGuire BE, et al. Psychological stress in early life as a predisposing factor for the development of chronic pain: Clinical and preclinical evidence and neurobiological mechanisms. J Neurosci Res 2017 Jun;95(6):1257-1270.

27. Eller-Smith OC, Nicol AL and Christianson JA. Potential Mechanisms Underlying Centralized Pain and Emerging Therapeutic Interventions. Frontiers in Cellular Neuroscience 2018; 12: 35.
28. Geertzen JH, Dijkstra PU, van Sonderen EL, et al. Relationship between impairments, disability and handicap in reflex sympathetic dystrophy patients: a long-term follow-up study. Clin Rehabil 1998; 12: 402-412.
29. Stewart DE and Yuen T. A systematic review of resilience in the physically ill. Psychosomatics 2011; 52: 199-209.
30. Faye C, McGowan JC, Denny CA, et al. Neurobiological Mechanisms of Stress Resilience and Implications for the Aged Population. Current Neuropharmacology 2018; 16: 234-270.
31. Albrecht A, Mueller I, Ardi Z, et al. Neurobiological consequences of juvenile stress: A GABAergic perspective on risk and resilience. Neurosci Biobehav Rev 2017; 74: 21-43.
32. Kaye-Tzadok A and Davidson-Arad B. Posttraumatic growth among women survivors of childhood sexual abuse: Its relation to cognitive strategies, posttraumatic symptoms, and resilience. Psychol Trauma 2016; 8: 550-558.
33. Rutter M. Resilience in the face of adversity. Protective factors and resistance to psychiatric disorder. Br J Psychiatry 1985; 147: 598-611.
34. Connor KM and Davidson JR. Development of a new resilience scale: the Connor-Davidson Resilience Scale (CD-RISC). Depress Anxiety 2003; 18: 76-82.
35. Kobasa SC, Maddi SR, Puccetti MC, et al. Effectiveness of hardiness, exercise and social support as resources against illness. J Psychosom Res 1985; 29: 525-533.
36. Seery MD, Holman EA and Silver RC. Whatever does not kill us: cumulative lifetime adversity, vulnerability, and resilience. J Pers Soc Psychol 2010; 99: 1025-1041.
37. Anonymous ©2013 Nederlandse Vereniging van Revalidatieartsen: De revalidatiearts, https://revalidatiegeneeskunde.nl/de-revalidatiearts (2013, accessed May 2018).
38. Bean DJ, Johnson MH, Heiss-Dunlop W, et al. Do psychological factors influence recovery from complex regional pain syndrome type 1? A prospective study. Pain 2015; 156: 2310-2318.

Summary

The aim of this thesis was to explore psychological aspects in rehabilitation. The influence of psychological and social factors within medicine was introduced in 1978 by Engel's biopsychosocial model. This model adds psychological and social influences to the biomedical model and gives room for the fact that body and brain influence each other. But research into effects of psychological interventions in medical research is scarce. As a psychologist in rehabilitation I realized that in general psychological influences on restrictions or other consequences of adversity, such as diseases or trauma, were hardly studied. The reason I ran into many questions in daily practice. This lack of information motivated me to find answers on at least some of these questions. The thesis presents five studies, a review and an opinion paper, seven chapters as result of my quest. For every chapter the research question, methods, results, conclusions, future research will be presented.

Quality of Life study, chapter 2

Question: What are the scores of rehabilitation outpatients on Quality of Life (QOL) and what is the influence of diagnosis and patient characteristics on those scores. *Methods:* 542 outpatients, referred to a rehabilitation psychologist. Referral diagnoses were "musculoskeletal", "chronic pain", "neurological" and "miscellaneous". Comparisons between groups were made for each of the four domains of the World Health Organization Quality of Life questionnaire abbreviated version (WHOQOL-BREF), scoring range 4-20. *Results:* In rehabilitation outpatients, scores on all WHOQOL-BREF domains were significantly lower than those of the general Dutch population. The differences between the rehabilitation outpatients and the general Dutch population on the psychological and social domain were small. Patients with chronic pain were found to exhibit a significantly lower QOL in all four domains when compared to the group of patients with musculoskeletal problems. *Conclusions:* The (negative) influence of chronic pain was stronger compared to musculoskeletal problems in all domains. *Limitations*: Only patients that were referred by the rehabilitation specialist to the rehabilitation psychologist were included*. Future research:* To explore the reason for the difference in QOL between different groups.

Cognitive dysfunction study, chapter 3

Question: What is the magnitude of cognitive dysfunction in rehabilitation outpatients and is cognitive dysfunction associated with patient characteristics, diagnosis, surgery, pain, anxiety, stress and depression? *Methods*: Cognitive functioning was assessed in 274 rehabilitation outpatients using the cognitive failure questionnaire and compared with the general Dutch population. Associations of gender, age, diagnosis, recent surgery, pain and stress coping ability with cognitive function were explored. Mediation of depression and anxiety was explored. *Results*: On average rehabilitation outpatients reported more problems compared to the general Dutch population, but the difference was small. High stress coping ability was protecting against cognitive failure, while there was a mediating effect of anxiety and depression. *Conclusions*: Patients with more depression or anxiety had more

cognitive problems. High resilience lowered this effect. The expected association with surgery or pain, found in other studies, was not confirmed in this study. One explanation of this difference in outcomes was, that in previous studies stress coping ability, depression and anxiety were not included in the analyses. *Limitations*: Only one (subjective) instrument was used to measure cognition. *Future research:* How to adapt rehabilitation programs to different levels of cognitive dysfunctions.

Prosthesis satisfaction review study, chapter 4

Question: Which factors influence patient satisfaction with a transtibial prosthesis and how is that measured. *Methods*: A literature search was performed in PubMed, Embase, PsycInfo, CINAHL, Cochrane, and Web of Knowledge databases up to Febuary 2018 to identify relevant studies. *Results:* Patient satisfaction was influenced by many different factors. Significance of the factors was related to gender, etiology, liner use, and level of amputation. Questionnaires assessed different aspects of satisfaction.
Conclusions: Patient satisfaction was influenced by many factors in different domains: Appearance, properties, fit, and use of the prosthesis, as well as aspects of the residual limb. Relevance of certain factors seems to be related to specific amputee patient groups, none of the questionnaires covers all factors.
Limitations: This review is limited to transtibial amputee patients, 12 studies, with an atypical population (predominately traumatic amputees).
Future research: Prosthesis satisfaction should be systematically evaluated by means of an assessment of all known factors influencing satisfaction.

Resilience in Complex Regional Pain Syndrome Type I (CRPS-I) study, chapter 5

Question: What is the association between resilience and post amputation outcomes, i.e. quality of life, pain, recurrence of CRPS-I and psychological distress? *Methods*: Twenty-six patients with an amputation related to CRPS-I filled in the Connor-Davidson Resilience Scale (CD-RISC), WHOQOL-Bref and the Symptom Checklist-90 Revised (SCL-90-R). An interview was conducted and a physical examination performed. Results were compared with reference groups from literature and a control group from the outpatient rehabilitation clinic of our medical center. *Results*: Resilience correlated significantly with all domains of the WHOQOL-Bref and negatively with all domains of the SCL-90-R. *Conclusions*: Compared with a control group, patients with an amputation because of CRPS-I had higher scores on resilience and QOL. *Limitations*: The cross sectional design and the small group limit the conclusions. *Future research*: The prognostic value of resilience in this patient group.

Association with outcome study, chapter 6

Question: Which psychosocial factors prior to amputation are associated with poor outcomes of amputation for longstanding therapy resistant CRPS-I? *Methods*: Between May 2008 and August 2015, 31 patients with longstanding therapy resistant CRPS-I were amputated. Before the amputation 11 psychological factors were assessed. In 2016, participants had a structured interview by telephone and filled out questionnaires to assess their outcome. In case of a perceived recurrence of CRPS-I a physician visited the patient to examine the symptoms. Associations between psychological factors and poor outcomes were analysed. *Results*: Four of the 11 predictors were associated with poor outcomes. The change in the worst pain experienced was associated with poor social support and pain before amputation. Resilience scores of participants who perceived an important improvement in mobility were higher compared to those who did not perceive an important improvement in mobility. Being involved in a lawsuit (Before the amputation) was associated with a recurrence in the residual limb (Bruehl criteria) and a psychiatric history was associated with a recurrence somewhere else. *Conclusions*: Poor outcomes of amputation in case of longstanding therapy resistant CRPS-I were partly predicted by psychological factors. Participants with adversity in childhood or stressful lives had the same outcome as patients without it. *Limitations*: The small sample and the lack of a control group and the many independent variables limit the conclusions. *Future research:* Include other variables like fear of movement or injury and pain related fear in studies and a control group to compare the results.

Outcome study, chapter 7

Question: What is the long-term outcome of amputation in patients with longstanding and therapy-resistant CRPS-I, regarding QOL, pain, recurrence of CRPS-I, use of a prosthesis and functioning in daily life? *Methods*: From May 2000 to September 2015, 53 patients underwent an amputation of a limb affected by long-standing, therapy-resistant CRPS-I at our institute. Forty-eight patients (40 women) participated in this study. Median age at time of diagnosis was 33.5 years (interquartile range (IQR), 20.3 to 40.0 years) and median interval between amputation and this study was 5.5 years (IQR, 3.0 to 11.0 years). Participants completed 5 questionnaires, a semi-structured interview was conducted and, if indicated, a physical examination was performed. For a subgroup (n=17) a longitudinal follow-up was performed since data was available from a previous study. *Results*: From the 48 participants, 44 reported an improvement in mobility, 40 an improvement in overall change and 37 a reduction in pain. Decrease in use of pain medication was reported by 30 participants. Recurrence of CRPS-I occurred in the residual limb of 1 participant and in another limb of 3 participants. *Conclusions*: Most improvement was reported for mobility, overall change and pain. Recurrence of CRPS-I was 8%. *Limitations*: A control group was missing and the questions used were subjective and assessed over a long time period, leaving room for errors, poor memory (recall bias) and cognitive dissonance. *Future research:* Prospective research with objective mobility measurements, preferably with a control group, is recommended.

Decision Paper, chapter 8

This position paper describes the decision making process of amputation in case of longstanding therapy resistant CRPS-I as is currently being done in the multidisciplinary team. This elective amputation is controversial and it is difficult to predict the outcome e.g. decrease in pain, increase in mobility and recurrence of the CRPS-I. This lack of prediction of the outcome led to research, however its quality till now is limited, due to small groups and a missing control group. By describing the decision making process, the team members became more aware of their considerations and decisions. They act more transparent and are open for discussion with colleagues and patients. This discussion can also help to design better future research.

Conclusion

Associations between psychological factors and rehabilitation were found. In this thesis resilience, cognition, social support, anxiety, depression and pain are associated with outcome (QOL) of rehabilitation outpatients. Integration of psychology in (rehabilitation) medicine will not only enrich the diagnostic opportunities but also increase the therapeutic options. The dare of Engel of 40 years ago is still the same, all medical specialists increase their skills but quality of collaborations has not increased. Hence we all need to widen our view.

Samenvatting

Introductie

Binnen de geneeskunde spelen psychologische aspecten een rol. Deze aanname werd al in 1978 door Engel beschreven, vlak voordat ik in de revalidatie ging werken. Engel merkte op dat artsen op het gebied van lichamelijke afwijkingen steeds meer kennis kregen en hun technische handelen vooruit ging, maar dat de tevredenheid van patiënten achterbleef. Hij stelde voor het medische model uit te breiden naar het biopsychosociale model. Hij dacht dat aandacht voor psychologische en sociale factoren naast de biologische wel die verbetering in tevredenheid zou kunnen brengen die hij miste.
In dit proefschrift is gekeken naar de invloeden van psychologische factoren binnen de revalidatie.
In de revalidatiezorg hebben patiënten meestal met tegenslag als ziekte, ongeluk of aangeboren afwijking te maken. De daaruit voortvloeiende beperkingen in het dagelijks functioneren vereisen acceptatie en aanpassing om een zo optimaal mogelijk bestaan te leiden, een bestaan met een voor diegene bevredigende kwaliteit van leven. Er is weinig onderzoek gedaan naar de invloed van psychologische factoren op die gevolgen van bovengenoemde tegenslagen. De 5 onderzoeken beschreven in dit proefschrift zijn voortgekomen uit vragen waar ik in de praktijk tegen aan liep. Deze onderzoeken zijn aangevuld met een systematische literatuur review om te weten wat er bekend is over factoren die tevredenheid van patiënten met een beenprothese kunnen beïnvloeden. Ook is een procedure artikel toegevoegd om de werkwijze van het team dat besluiten neemt over amputaties die medisch gezien niet (altijd) noodzakelijk zijn, wereldkundig te maken en ter discussie te stellen.
Hieronder zijn deze 7 hoofdstukken kort beschreven.

Kwaliteit van leven, hoofdstuk 2
Als patiënten behandeld worden is het uiteindelijk de vraag of ze er beter van worden, maar wat is “beter worden” eigenlijk; daar zijn verschillende meningen over. Kwaliteit van leven metingen geven informatie hoe patiënten hun kwaliteit van leven beoordelen. Het resultaat van de behandeling reflecteert zich in kwaliteit van leven en er is algemene consensus dat met kwaliteit van leven metingen het resultaat van de behandeling is te evalueren. De kwaliteit van leven metingen maken het ook mogelijk (groepen) mensen met elkaar te vergelijken. De meting beantwoordt niet direct de vraag of iemand “beter” is geworden maar het meet het indirect. Dit onderzoek beschrijft 542 patiënten van de polikliniek revalidatie van het UMCG die vragen over hun kwaliteit van leven beantwoorden. Kwaliteit van leven wordt ingedeeld in 4 domeinen: het fysieke domein, het psychologische domein, het sociale domein en de omgeving. Het bleek dat mensen met verschillende lichamelijke (fysieke) problemen lager scoorden op het fysieke domein maar ook lager op het psychologische domein dan mensen zonder lichamelijke problemen. Chronische pijnpatiënten scoorden op het psychologische domein lager dan andere revalidatiepatiënten.

Cognitieve disfunctie, hoofdstuk 3
Patiënten, van de polikliniek revalidatie van het UMCG, klagen over cognitieve stoornissen zoals een slecht functionerend geheugen of moeite hebben met concentreren. Dit onderzoek heeft geanalyseerd hoeveel patiënten een cognitieve stoornis ervaren en welke factoren van invloed zijn op deze ervaren cognitieve stoornis. De factoren die zijn onderzocht zijn: eigenschappen van patiënten, de diagnose, een doorgemaakte operatie, pijn, angst, depressie of stress. Het onderzoek omvatte 274 patiënten die werden verwezen naar de revalidatie psycholoog. Het bleek dat in deze verwezen revalidatiepatiënten meer ervaren cognitieve stoornissen voorkwamen dan in de algemene Nederlandse bevolking. Het bleek dat angstige of depressieve patiënten meer cognitieve stoornissen ervoeren dan patiënten die dat niet waren. Het effect van angstige of depressieve patiënten op ervaren cognitieve stoornissen was kleiner bij patiënten die een hoge veerkracht hadden (goed kunnen omgaan met stressvolle situaties). Pijn of een operatie had geen effect op de ervaren cognitieve stoornissen.

Tevredenheid met een prothese, hoofdstuk 4
De tevredenheid met een onderbeenprothese hangt van vele factoren af maar een overzicht van alle factoren bestaat niet omdat meestal één of slechts enkele aspecten worden onderzocht. In een systematische literatuurreview is geïnventariseerd welke factoren in het verleden onderzocht zijn in relatie tot en tevredenheid met een onderbeenprothese. Daarnaast werd geanalyseerd hoe deze factoren werden gemeten. De gevonden factoren konden worden verdeeld in 5 domeinen: het uiterlijk van de prothese, de eigenschappen, de pasvorm, het gebruik en de invloed van de prothese op de stomp. Het bleek dat de gebruikte vragenlijsten nooit alle factoren in kaart brachten en dat sommige factoren voor de ene groep belangrijker waren dan voor de andere groep patiënten. Bijvoorbeeld mannen hechten vaker belang aan functie van de prothese en vrouwen vaker aan het uiterlijk van de prothese. Jonge mensen vonden het vaker belangrijk dat met de prothese gesport kon worden terwijl ouderen het dagelijks gebruik belangrijk vonden.

Veerkracht in complex regionaal pijn syndroom-I (CRPS-I), hoofdstuk 5
In de volgende drie hoofdstukken wordt gekeken naar het resultaat van een amputatie bij chronische therapie resistente CRPS-I. Dat is een syndroom waarbij een persoon onverklaarbare ernstige pijn in een lichaamsdeel ervaart (vaak hand of voet) maar ook worden andere verschijnselen ervaren zoals zwelling, veranderde haargroei, zweten of steenkoud zijn van dat lichaamsdeel. Door een amputatie kan de ernst van de verschijnselen worden beïnvloed.
Bij 26 patiënten die werden geamputeerd met als doel afname van klachten van CRPS-I, is onderzocht of er een verband was tussen veerkracht en kwaliteit van leven. Het bleek dat de mate van veerkracht een positief verband had met kwaliteit van leven. Patiënten die hoog scoorden op veerkracht hadden tenminste een jaar na de amputatie een betere kwaliteit van leven en minder stress verschijnselen.

Psychologische factoren die het resultaat van een amputatie voor CRPS-I beïnvloeden, Hoofdstuk 6
Bij 31 patiënten werden, voor de amputatie van de door CRPS-I getroffen ledemaat, 11 psychologische factoren gemeten en ten minste een jaar na de amputatie werden ze bevraagd op pijn, mobiliteit en terugkeer van de CRPS-I. Vier van de 11 factoren bleken een verband te hebben met het resultaat van de amputatie. Bij twee factoren was er sprake van een duidelijk verband. Bij patiënten die veel sociale steun ontvingen was de afname van pijn sterker dan bij mensen die minder steun ontvingen. Bij mensen met een bovengemiddelde veerkracht was het gemak waarmee men zich verplaatst in de omgeving (mobiliteit) sterker vooruit gegaan dan bij mensen met een beneden gemiddelde veerkracht. In tegenstelling tot wat verwacht was bleek dat patiënten die veel tegenslag hadden gehad niet een slechter resultaat van de amputatie hadden dan patiënten met minder tegenslag.

Resultaat van een amputatie bij CRPS-I, hoofdstuk 7
Bij 48 patiënten is het resultaat van een amputatie vanwege CRPS-I, tenminste één jaar na de amputatie, geëvalueerd. In 2016 zijn alle patiënten die in Groningen zijn geamputeerd vanwege een CRPS-I geïnterviewd en werden vragenlijsten afgenomen. Dit onderzoek was 7 jaar eerder ook al eens uitgevoerd maar nu kon worden onderzocht wat de lange termijn uitkomsten van deze groep patiënten was.
Van de 48 patiënten vertelden 44 dat ze mobieler waren geworden. Dit laatste lijkt misschien raar na een amputatie, maar de meeste patienten hadden zoveel pijn dat ze niet veel meer konden doen. Bovendien waren ze zo bang dat iemand anders tegen ze aan zou lopen (gaf nog meer pijn) dat ze liever binnenshuis bleven. Vier en dertig patiënten rapporteerden een afname van pijn. Er waren 4 patiënten die opnieuw CRPS-I hadden gekregen. Algemene conclusie was dat in drie kwart van de patiënten de klachten (pijn en beperkte mogelijkheden zich te verplaatsen) waren afgenomen.

Beslissen tot een amputatie bij CRPS-I, hoofdstuk 8
Een beslissing nemen om te amputeren vanwege therapie resistente CRPS-I is en blijft een moeilijke procedure. Deze beslissing wordt genomen in een team van specialisten uit verschillende disciplines. Het betreft een revalidatiearts, een (vaat)chirurg, een anesthesist, een fysiotherapeut en een psycholoog. Het beschrijven van de procedure waarbij iedere specialist werd uitgenodigd de denkbeelden van dat specialisme te beschrijven leverde veel discussies op en meer inzicht in elkaars denken. Als gevolg daarvan werden aanpassingen in de procedure doorgevoerd. Het een en ander leidde tot een meer transparante procedure gebaseerd op kennis en kunde van meerdere disciplines. Besluiten die met de patiënt worden gedeeld kunnen nu beter onderbouwd worden. Door het publiceren van deze procedure kunnen andere specialisten buiten het team, die het lang niet altijd eens zijn met amputatie, ook mee denken en discussiëren.

Conclusie

Veerkracht, cognitie, sociale ondersteuning, angst, depressie en pijn zijn geassocieerd met resultaten (kwaliteit van leven) van behandeling van revalidatiepatiënten. Psychologisch onderzoek levert andere diagnostische gegevens en daarmee andere aangrijpingspunten voor de behandeling van de revalidatiepatiënt dan de medische benadering.

Dankwoord

Zoals sommigen weten, is mijn schrijven net even erger dan mijn zingen: het klopt gewoon niet. Als ik het alleen had moeten doen, dan was dit boekje er nooit gekomen. Het fijne aan promoveren is, dat je door je promotors en vele anderen wordt geholpen. Hierdoor heeft het schrijven van dit proefschrift mij veel gebracht. Zo kreeg ik opeens tijd voor onderzoek dat al lang geleden was ingezet, voor het lezen van vakliteratuur, voor het verzamelen van data en vooral om onbeantwoorde vragen in mijn werkveld richting te geven, te toetsen en af te ronden. Ik heb deze periode ervaren als een, waarin de gunfactor een grote rol speelde en daar bedank ik iedereen hartelijk voor. Misschien hebben sommigen van jullie zich tussen de regels door al herkend, anderen hebben wellicht onbewust een rol gespeeld.
Een paar mensen bedank ik in het bijzonder. Dat zijn logischerwijs mijn promotores Pieter Dijkstra en Jan Geertzen en om te beginnen met Hanneke.
Zoals jij mij bijstond in het begin (gunfactor) en tegen het eind (maak het maar af) van mijn promotie onderzoek, zo zijn ook de eerste en de laatste bladzijde natuurlijk aan jou gewijd. Toen ik met het idee van promoveren kwam, toen wilde jij wel taken van mij overnemen. Ondanks de tegenslagen die je keer op keer te verwerken kreeg, bleef je mij die ruimte geven. Ook heb je mij, met je gevoel voor taal, op kritische momenten steeds weer vlot getrokken. Bovendien maakte je de prachtige cover. Dank voor alles Han. We prijzen ons gelukkig dat we al bijna 45 jaar samen zijn, ik hoop van harte dat ons nog wat jaren gegund zijn.
Pieter, met jou heb ik het meeste te maken gehad tijdens dit traject. Jij kwam met het idee en ik zei geen nee. Ik heb deze periode ervaren als een fijne samenwerking, een samenwerking die zich kenmerkte door jouw begeleiding van mij. Als ik uit koers dreigde te raken of raakte, loodste jij me weer richting haven; wat anders te verwachten van een zeiler. Steeds weer kwam je, met vers lood in de schoenen, met tips voor de richting. Je gaf me inzicht in wat er in een onderzoek moest staan en wat weggelaten kon worden. Werd dit me te ingewikkeld, dan deed je het nog een keer voor en gaf me vervolgens het roer weer in handen. En daarnaast hadden we dierbare gesprekken, konden we echt gek doen, gaven we elkaar een dikke knuffel, kwam je met cadeaus, hielp je met de bouw van de kas, liet je mij een zeearend zien, en alles altijd met dezelfde aanstekelijke energie. Dank Pieter, veel dank.
Veel steun heb ik aan jou gehad Jan. Ik deelde je optimisme over de snelheid van het promoveertraject. Ik dacht dat een promotie, net zoals het verbouwen van een huis, het spitten van de tuin, het schrijven van een hoofdstuk, of het voorbereiden van een lezing, sneller zou gaan. Misschien is dat ook zo, als niet alles parallel was gepland deze jaren. Ik heb me vaak verbaasd over de snelheid, waarmee je met correcties en adviezen terugkwam. Ik ben blij dat we naast de promotie ook vergaderden in Utrecht of in Engeland, een hoofdstuk voor een boek schreven, samenwerkten rond de CRPS-I patiënten en allerlei andere krenten uit de pap wisten te halen. De manier, waarop jij voor patiënten opkomt en de samenwerking met andere professionals opzoekt, waardeer ik ontzettend. Hartelijk bedankt voor dit alles.
Dan wil ik graag Chantal (niet haar echte naam) en al die andere patiënten, die mij steeds weer voor raadsels stelden, bedanken. De patiëntenzorg vormde de basis

waar mijn onderzoek en onderwijs uit voortkwamen, wetende dat de praktijk vaak net weer anders is dan de theorie. Net wanneer ik dacht dat je voor fantoomgevoel een amputatie moet hebben gehad, ontmoette ik iemand met een verlamde arm die slap langs het lichaam hing. Hij ervaarde als fantoomgevoel een arm met de elleboog gebogen. De veerkracht en inventiviteit die patiënten tijdens de behandeling lieten zien motiveerden mij om bijna 40 jaar met veel plezier in de revalidatie te werken. Dank voor al die verhalen en levenslessen.

En dan zijn er diegenen, die hebben geholpen bij het verhelderen en verwoorden van mijn gedachten: Nyckle, Hanneke, Maerian, Sacha, Sonja en zij, die een bijdrage hebben geleverd aan een artikel: Irene, Bram, Vera, Marjon, Marlies, Jelmer, Edwin, Clark, André, Frank en Hilde. De leden van de leescommissie beoordeelden in de slotfase de thesis. Op steun voor de praktische zaken kon ik op Leonie, Sietke, Sietske en Truus rekenen. En Inge, Mitzy, Petra, Dorien, Miranda, Berend, Hanneke, Marga, Grytsje en andere collega's ondersteunden mij door iets te regelden, een kaartje te sturen of een schouderklop te geven. Allen bedankt!
Tot slot ben ik dankbaar dat mijn lieve kinderen mij op deze dag begeleiden. Bram en Irene, zo verschillend, beiden met dezelfde uitwerking: gezelschap waar je bij wilt horen en waar je blij en optimistisch van wordt. Dank dat jullie er (deze dag) zijn, samen met Freek en Sacha en natuurlijk Vic.

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2019

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Sleep and fatigue offshore
(prof U Bültmann, prof S Brouwer, dr MR de Boer)

Maters GA
Lungs under a cloud; psychological aspects of COPD
(prof R Sanderman, dr JB Wempe, dr G Pool)

Timmeren EA van
Physical health in adults with severe or profound intellectual and motor disabilities
(prof CP van der Schans, prof HMJ van Schrojenstein Lantman-de Valk, prof AAJ van der Putten, dr A Waninge)

Berghuis KMM
Age-related changes in neural plasticity after motor learning
(prof T Hortobayi, prof G Koch, dr CAT Zijdewind)

Ploegmakers JJW
Grip on prognostic factors after forearm fractures
(prof SK Bulstra, dr CCPM Verheyen, dr B The)

Sas AA
(Genetic) epidemiology of inflamation, age-related pathology and longevity
(prof H Snieder, dr H Riese)

Joustra ML
Similar but different; implications for the One versus Many Functional Somatic Syndromes Discussion
(prof JGM Rosmalen, prof SJL Bakker, dr KAM Janssens)

Nandi T
Neural control of balance in increasingly difficult standing tasks
(prof T Hortobagyi, prof BE Fisher, dr CJM Lamoth, dr GJ Salem)

Fontanella F
Antenatal diagnosis and management of fetal megacystis and lower urinary tract obstruction
(prof CM Bilardo, prof D Oepkes)

2018

Osterthun R
Outcomes after spinal cord injury
(prof MWM Post, dr F van Asbeck)

Dammen L van
Women's health and wellbeing: the roles of early life adversity, stress and lifestyle
(prof A Hoek, prof TJ Rosenboom, dr H Groen, dr SR de Rooij)

Dorland-Pel HF
Work functioning in cancer patients: looking beyond return to work
(prof U Bültmann, prof AV Ranchor, dr FI Abma, dr CAM Roelen)

Simoons M
Somatic monitoring of patients with mood and anxiety disorders; problem definition, implementation and further explorations
(prof EN van Roon, prof RA Schoevers, dr H Mulder, dr HG Ruhé)

Bouma AJ
The barrier-belief approach; a new perspective of changing behavior in primary care
(prof RL Diercks, prof A Dijkstra, prof CP van Wilgen)

Looijmans A
Lifestyle interventions in patients with a severe mental illness; addressing self-management and living environment to improve health
(prof RA Schoevers, prof RP Stolk, dr F Jörg, dr E Corpeleijn)

Phí XA
Breast cancer screening in women at elevated risk; comparative evaluation of screening modalities to inform practice
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