Supporting caregivers of people with Amyotrophic Lateral Sclerosis

Jessica de Wit

ISBN: 978-90-830137-0-1
Cover image: Paniti Alapon | Shutterstock.nl
Cover design: proefschriftenprinten.nl
Layout and printing: proefschriftenprinten.nl

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Supporting caregivers of people with Amyotrophic Lateral Sclerosis

Het ondersteunen van naasten van mensen met Amyotrofische Laterale Sclerose

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
op gezag van de rector magnificus, prof. dr. H.R.B.M. Kummeling,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen op
woensdag 9 oktober 2019 des middags te 2.30 uur

door

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geboren op 22 maart 1988
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The studies in this thesis were financially supported by The Netherlands ALS Foundation.
The study described in chapter 3 was supported by The Netherlands Organization for Health Research and Development (ZonMw) and the Prinses Beatrix Spierfonds.

Financial support for the printing of this thesis has been generously provided by Stichting de Hoogstraat Onderzoeksfonds Utrecht.

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CHAPTER 1

General introduction

Amyotrophic Lateral Sclerosis

Amyotrophic Lateral Sclerosis (ALS) is a fatal neurodegenerative disorder, characterized by progressive upper and lower motor neuron loss.[1] Symptoms of lower motor neuron loss include muscle weakness, atrophy and fasciculations, while upper motor neuron loss leads to spasticity and hyperreflexia. [2] Symptom onset is usually presented as muscle weakness, which may start in the hands or legs or be manifested by difficulties in speech.[3] Eventually, these symptoms progress gradually to paralysis and spread to other body parts, culminating in death from respiratory failure. The speed of the disease progression is highly variable between patients and the average survival is 3-4 years after symptom onset.[4] Approximately 50% of ALS patients also show cognitive or behavioral changes next to the physical disabilities.[5, 6] Apathy and loss of sympathy are the most common behavioral changes.[7] Fluency, language, social cognition, and executive function are the cognitive domains that are most often affected.[8] The presence of cognitive and behavioral changes becomes more frequent in more advanced disease stages.[9] Up to 15 % of patients fulfill the criteria of the diagnosis frontotemporal dementia (FTD).[5, 6]

Progressive Muscular Atrophy (PMA)[10] is considered as a rare subtype of ALS.[11] While ALS affects both upper and lower motor neurons, PMA only affects lower motor neurons. However, in the first 5 years after diagnosis, clinical evidence of upper motor involvement becomes apparent in about 20% of the patients, leading to an ALS diagnosis.[11] Cognitive and behavioral changes are also present in patients with PMA.[12] The median survival duration of patients with PMA is significantly longer than that of patients with ALS (48.3 months vs. 36 months).[11]

Professional care for patients with ALS or PMA

To date, no cure or medical intervention is available to stop the disease progression in patients with ALS or PMA. Since there is no cure for patients, care is focused on the quality of life of these patients and providing optimal support.[13] In the Netherlands, care for ALS and PMA patients is organized around three phases: the diagnostic phase coordinated by the neurologist, the rehabilitation phase coordinated by the rehabilitation physician, and the terminal phase coordinated by the general practitioner.[14] During the rehabilitation phase the patient receives support from a multidisciplinary ALS care team including a rehabilitation physician, a physical therapist, an occupational therapist, a speech pathologist, a dietician, a social worker and sometimes also a psychologist. Additionally, patients often receive professional care at home to be supported in their daily functioning (e.g. washing and dressing).

Informal care for patients with ALS or PMA

Informal care refers to the provision of care to an individual in the family or social network that has physical, psychological or developmental needs.[15] In ALS and PMA, the majority of care tasks are not performed by professionals, but by informal caregivers, such as partners or children.[16] Patients with ALS or PMA become increasingly impaired and dependent on their

environment and the amount of care that is needed accumulates during the disease course.[17] Patients may need support in all aspects of their daily functioning such as dressing, toileting, eating, communication and mobility.[16] Family members or friends often take up these care roles without formal preparation, knowledge, resources or skills needed to perform care tasks.[17] They can spent up to 15 hours a day on providing care.[16] During the disease course they require to manage multiple assistive devices such as wheelchairs, gastrostomy feeding devices, augmentative communication devices, and breathing devices.[7,18] Accomplishing these tasks can require many hours of time and can restrict participation in caregivers' own valued activities, such as work, leisure, or family life.[19, 20] Most patients with ALS die at home after an intense period of care.[21]

Psychological distress and caregiver burden in informal caregivers of patients with ALS or PMA

Providing care has strong consequences for the lives of informal caregivers including financial, social and privacy limitations.[22] Studies show a significant increase of caregiver burden over time in caregivers of patients with ALS.[23] Caregivers also express feelings of psychological distress[24], however, not all caregivers experience feelings of distress or burden. It is still unclear which factors explain the development of distress and caregivers burden in these caregivers.

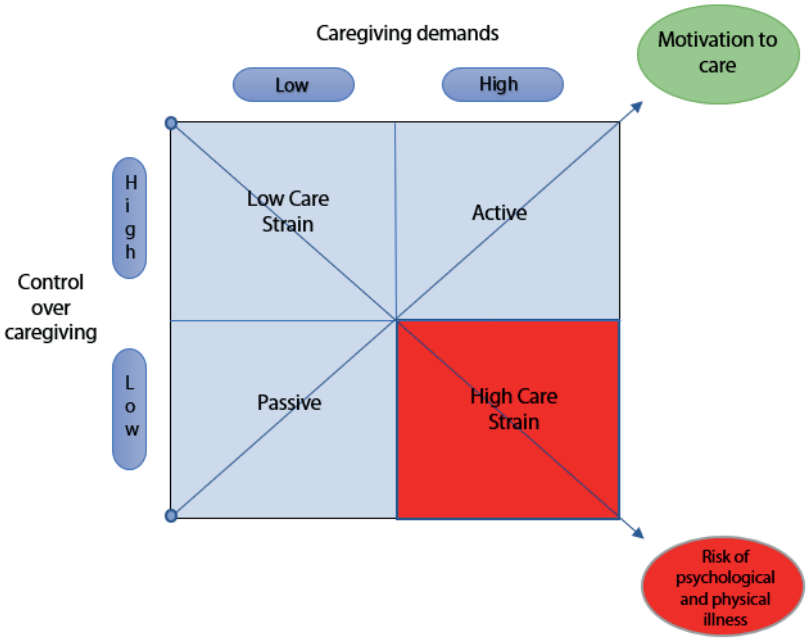

Figure 1. Control-demand model applied to the caregiver situation

A possible explanation for the development of psychological distress in caregivers is offered by the demand and control model (see figure 1).[25, 26] This model is originated from occupational psychology and is applied to informal caregiving.[25] According to the model, the two principle variables determining caregiver distress are the physical and psychological *demands* that are placed on caregivers and the *control* over fulfilling these caregiving demands. When ALS or PMA progresses, physical and psychological demands will increase and the skills of the caregiver will be challenged. High caregiving demands and low feelings of control over caregiving are associated with worse physical and psychological health outcomes in caregivers.[25, 27]

This challenging caregiving situation might result in physical and mental health problems in caregivers. Worsening of caregivers' health might affect the amount and quality of care they provide to the patient and ultimately might result in an earlier placement in a care home or a hospice.[28] Furthermore, research shows that the wellbeing of patients and caregivers is related[29], which indicates that improving the wellbeing of caregivers may also improve the wellbeing of patients.

Professional care for informal caregivers of patients with ALS or PMA

International guidelines for the management of ALS recommend to consider caregivers' health needs and to provide physical, psychological and spiritual support to caregivers when needed.[30] In the Netherlands, caregivers who struggle with their situation can receive support from a social worker or psychologist from the multidisciplinary ALS care team. However, psychosocial support is not yet structurally offered to all caregivers. Since there are no clear psychosocial guidelines, each multidisciplinary ALS care team organizes support for caregivers differently. Professionals from the multidisciplinary ALS care teams do not have specific tools to support caregivers of people with ALS or PMA. Although there is a need for psychological interventions to support these caregivers[31-33] , there are currently no psychosocial interventions for caregivers of people with ALS available. Since caregivers of patients with ALS and PMA are often preoccupied with the care for the patient, receiving care in an accessible and time efficient manner is crucial. Blended care combines face-to-face healthcare with an online intervention and enables caregivers to receive support where and when they prefer.[34]

Aims of this thesis

The overall aim of this thesis is to improve the support for caregivers of people with ALS or PMA in order to enhance their wellbeing. The subaims of this thesis are:

1. To unravel which caregiver and patient factors are related to caregiver burden and psychological distress in caregivers of people with ALS or PMA.
2. To increase knowledge about the support needs of caregivers of people with ALS or PMA.
3. To develop a blended support program for caregivers of people with ALS or PMA and evaluate the support program both quantitative and qualitative.

General outline of the thesis

Part 1 Factors related to caregiver burden and psychological distress

- Chapter two describes the results of a systematic review on factors related to caregiver burden in caregivers of people with ALS.
- Chapter three describes the results of a study on the development of psychological distress over time and factors related to psychological distress in caregivers of people with ALS.
- Chapter four describes the applicability of the demand and control model on the situation of caregivers of people with ALS or PMA.

Part 2 Support needs of caregivers

- Chapter five presents a qualitative study on the support needs of caregivers of people with ALS.

Part 3 A blended support program: ALS caregiver support

- Chapter six presents the protocol of a randomized controlled trial investigating the effectiveness of a blended support program based on Acceptance and Commitment Therapy for partners of people with ALS or PMA. The aim of the program is to increase feelings of control over caregiving in order to decrease feelings of psychological distress.
- Chapter seven discusses the outcomes of the randomized controlled trial evaluating the effectiveness of the support program for partners of people with ALS or PMA compared to a waiting list control group.
- Chapter eight describes the qualitative evaluation of caregivers' experiences with the support program.
- Chapter nine presents a general discussion describing the main findings of the studies, clinical implications and recommendations for further research.

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PART 1

Factors related to caregiver burden and psychological distress

CHAPTER 2

Caregiver burden in Amyotrophic Lateral Sclerosis: A systematic review

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Palliative Medicine. 2018, 32(1), 231-245

Abstract

Background: Informal caregivers of patients with Amyotrophic Lateral Sclerosis (ALS) experience increased levels of caregiver burden as the disease progresses. Insight in the factors related to caregiver burden is needed in order to develop supportive interventions.

Aim: To evaluate the evidence on patient and caregiver factors associated with caregiver burden in ALS informal caregivers.

Design: A systematic review.

Data sources: Four electronic databases were searched up to 2017. Studies that investigated quantitative relations between patient or caregiver factors and caregiver burden were included. The overall quality of evidence for factors was assessed using the Grading of Recommendations Assessment, Development and Evaluation approach.

Results: Twenty-five articles were included. High quality of evidence was found for the relation between caregiver burden and the factor 'behavioral impairments'. Moderate quality of evidence was found for the relations between caregiver burden and the factors 'feelings of depression' of the caregiver and 'physical functioning' of the patient. The remaining rated caregiver factors – 'feelings of anxiety', 'distress', 'social support', 'family functioning' and 'age' – and patient factors – 'bulbar function', 'motor function', and 'respiratory function', 'disease duration', 'disinhibition', 'executive functioning', 'cognitive functioning', 'feelings of depression' and 'age' – showed low to very low quality of evidence for their association with caregiver burden.

Conclusion: Higher caregiver burden is associated with greater behavioral and physical impairment of the patient and with more depressive feelings of the caregiver. This knowledge enables the identification of caregivers at risk for caregiver burden and guides the development of interventions to diminish caregiver burden.

Introduction

Amyotrophic Lateral Sclerosis (ALS) is a fatal neurodegenerative disease that causes severe restrictions in physical functioning. Patients suffer from progressive weakness of voluntary muscles and approximately 30-50 percent of the ALS patients experience cognitive impairments.[1, 2] The disease leads to an increasing need for care; a major role in this care process is fulfilled by informal caregivers (family, friends and neighbors).

Caring for an ALS patient is a demanding task. During the course of the disease the patient may require support with all activities of daily living such as eating, transportation and medical care.[3] Furthermore, caregivers often struggle with accepting this fatal disease, their increased responsibilities, concerns about the future and feelings of guilt.[4] Findings from longitudinal studies indicate that caregivers of patients with ALS experience increasing levels of physical and emotional distress, often referred to as caregiver burden.[5, 6] Caregiver burden is defined as the impact on the emotional health, physical health, social life, and the financial status of the caregiver as a result of adopting the caregiving role.[7]

The well-being of caregivers is essential in ALS care; their capacity proves to be an important factor in enabling ALS patients to remain at home until the end of their lives rather than going into a care facility.[8] Moreover, studies show a high concordance between the well-being of the patient and that of the caregiver, indicating that a reduced well-being of the caregiver can negatively impact the well-being of the patient.[9-11]

Knowledge about which factors relate to caregiver burden is needed in order to develop interventions to support caregivers. During the last decade, three reviews have been published concerning the wellbeing of ALS caregivers, but a comprehensive overview of both modifiable and non-modifiable patient and caregiver factors influencing caregiver burden is lacking.[12-14] The objective of the present study, therefore, was to systematically review published literature to investigate which caregiver and patient factors are related to caregiver burden in informal caregivers of patients with ALS.

Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines,[15] see Appendix 1. This systematic review has been registered with PROSPERO 2015 CRD42015019842.

Search strategy

The electronic databases PsycINFO, Medline (PubMed), CINAHL and EMBASE were systematically searched using the following keywords, along with synonyms: 'amyotrophic lateral sclerosis', 'burden' and 'caregiver'. A clinical librarian was consulted regarding the search strategy, which is presented in Appendix 2. No constraint was placed on the year of publication; searches were conducted up to December 2016. Additionally, references were checked for relevant publications. To make sure that no relevant papers had been missed, we sent a list of papers identified through the search to researchers in the field of ALS care for their review.

Inclusion criteria

Studies that investigated quantitative relationships between caregiver or patient factors and caregiver burden in informal ALS caregivers were included. Factors had to be explicitly defined and in case of self-reported constructs measured with a validated questionnaire or a clearly described single question. Burden had to be assessed with a total caregiver burden construct. Only full-text articles, published in peer reviewed journals, in English, Dutch or German were considered eligible.

Exclusion criteria

Mixed sample studies – studies where caregivers of patients with different diagnoses are grouped together- were excluded, unless subsample analysis was performed for ALS caregivers. Studies that described the association solely with subscales of burden measures, or studies that combined burden with other outcomes measures into one overarching outcomes measure, were not taken into account. Intervention studies, qualitative studies, reviews and case reports were excluded.

Study selection

The titles and abstracts of the articles were independently screened for relevance by two reviewers (JW and AG); relevant publications, potentially eligible for inclusion, were read in full text by two reviewers (JW and LB). Disagreements were resolved by discussion until consensus was reached. Authors of the studies in the review were contacted by e-mail when information was missing.

Risk of bias assessment

The risk of bias of the included studies was assessed independently by the two researchers who assessed the full text articles (JW and LB). The Methodological Quality Assessment List,[16, 17] an 8-point checklist that yields a total score between 0 (low methodological quality) and 8 (high methodological quality), was used (Appendix 3). Since this checklist was originally applied to research on patients, the relevant characteristics to score item 3 'external validity' were changed into 'caregiver age, -gender, type of relationship with patient, physical functioning of the patient and time since patient's diagnosis'. Studies with a total score below 3 were excluded from the quality of evidence assessment. In case of disagreement, a third author was consulted.

Data synthesis

Data were independently extracted from eligible papers by two researchers (JW and LB) using structured data forms that were developed for this study and included key components of the study characteristics, study results and methodological quality of the studies. Due to the diversity of outcome measures and factors included in the study, a meta-analysis was not possible. Bivariate and multivariate associations were described separately in terms of correlation coefficients (*R)* and standardized β-coefficients (β). In studies that applied a logistic regression, the odds ratio (*OR)* was presented. Factors were grouped into patient and caregiver characteristics and subsequently thematically categorized.

Quality of evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess the overall quality of evidence for each factor measured in at least three studies (Appendix 4).[18] Two researchers (JW and LB) rated the factors on the GRADE criteria study limitations (here we used the Methodological Quality Assessment List), inconsistency, indirectness, imprecision and publication bias. The criteria 'dose effect' and 'moderate/large effect' were omitted, since these criteria were not relevant for the quality of evidence in our review. The overall quality of evidence was classified as high, moderate, low or very low.

Results

Studies selected

The search identified a total of 1126 possibly relevant articles. After the removal of duplicates and the abstract and full text screening, a total of 25 studies were left for inclusion in the review (Fig. 1). Two study samples were described in two articles each.[19-22] Since these articles investigated different factors in relation to burden, they were retained for review.

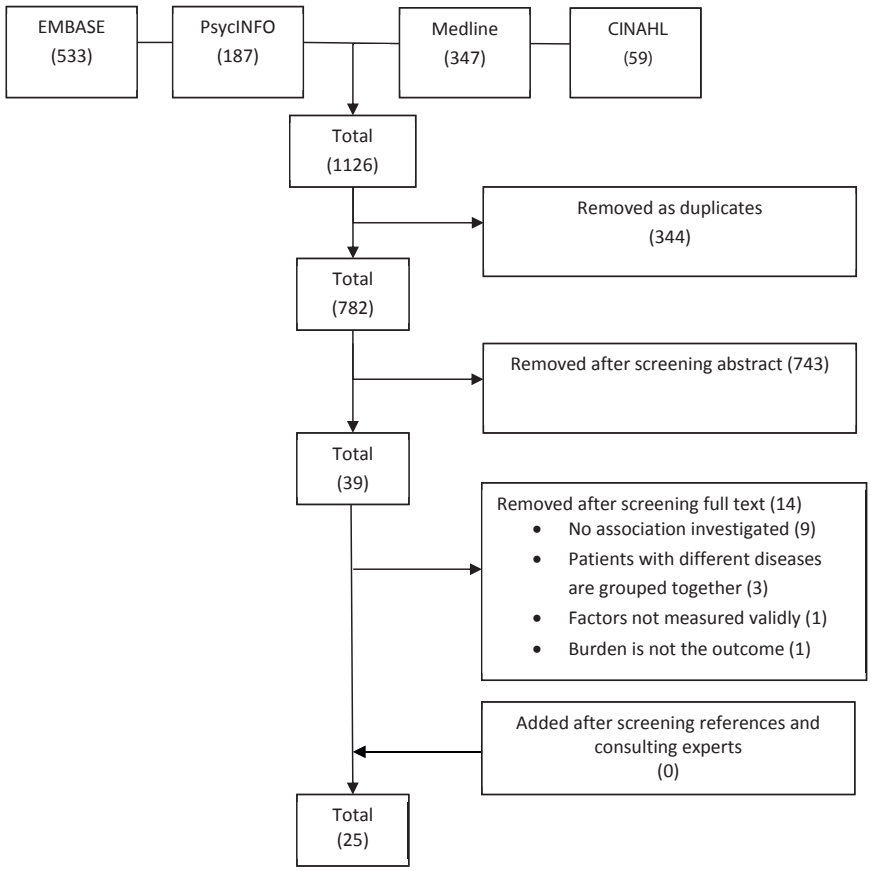

Figure 1. Search flowchart

Risk of bias

The methodological quality scores of the studies ranged from 2 to 7 out of a maximum of 8 (high quality) points (Appendix 5). One study scored a low total score, indicating a high risk of bias, and was not incorporated in the quality of evidence assessment.[23] The following items of the Methodological Quality Assessment List were not met by the majority of the studies: study participation, proportion sample size versus factors and confounding bias.

Description of studies included

The key characteristics of each study are presented in Table 1. The included studies were published in 8 different countries between 1998 and 2016 and the majority was published in the last decade. A total of 20 studies used a cross-sectional design and 5 studies a longitudinal design. A total of 22 studies investigated univariate associations; in ten studies, associations were explored

in multivariate models. The study samples ranged from 19[19, 20] to 415 caregivers.[24] Among the studies that reported the caregiver's relationship with the patient ($n = 22$), partners dominated the sample (range 63- 100%), with two studies recruiting partners only. Other relationships included children, siblings, parents, friends, neighbors and other relatives. Caregivers were predominantly female and the mean age of caregivers varied from 48 to 61 years. The mean time since disease onset ranged from 15 to 40 months.

Measures of burden

Across studies, five different validated measures of caregiver burden were used (Zarit Burden Interview ($n = 11$);[40] Caregiver Burden Inventory ($n = 6$);[41] Caregiver Strain Index ($n = 2$);[42] Burden Scale for Family Caregivers ($n = 1$);[43] Caregiver Burden Scale ($n = 1$))[44] and two studies used a number of selected items of the Zarit Burden Interview (see Appendix 6). Two studies used a single item measurement to measure burden.[45]

Studied factors in relation to caregiver burden in ALS caregivers

Overviews of the studied caregiver and patient factors that were investigated in relation to caregiver burden are presented in Table 2 and Table 3. Caregiver factors were grouped into the following categories: emotional functioning, social environment, demographics, personal factors, physical health and caregiving time. Patient factors were categorized into physical health, behavioral impairments, cognitive impairments, emotional functioning, personal factors, demographics and social environment.

Evidence for factors related to caregiver burden

Caregiver factors

The synthesis of evidence for the caregiver factors using the GRADE criteria, resulted in a rating of moderate quality of evidence for the relationship between higher caregiver burden and 'feelings of depression' (see Table 4). Low quality of evidence was found for the relations between higher caregiver burden and the factors 'anxiety', 'distress' and 'age'. The social environment factors 'social support' and 'family functioning' showed very low quality of evidence as factors associated with lower caregiver burden.

Factors within the categories personal factors, physical health of the caregiver and caregiving time were investigated in fewer than three studies and could not, therefore, be rated with the GRADE.

Patient factors

The synthesis of the evidence for the patient factors led to a rating of high quality evidence for the relationship between higher caregiver burden and 'behavioral impairments'. This factor represents total scores of questionnaires that measure behavioral impairments in patients, which

Table 1. The summary of included studies

Authors (Year)	Country	Design (Follow up)[1]	Caregiver sample n (% female)	Spouse of the patient (%)	Age in years caregivers Mean (sd)	Time since onset (o) time since diagnosis (d) Mean (sd) months	ALSFRS Mean (sd)
Andrews (2016) [25]	Australia	Cross-sectional	40 (78)	n.r.	56 (14.5)	26 (14.2), o	35.3 (8.9)[R]
Bock (2016) [26]	USA	Cross-sectional	86 (n.r.)	n.r.	n.r.	26 (48.6), o*	33.5 (11.1)[R*]
Burke (2015) [27]	Ireland	Cross-sectional	33 (66)	81.3	58 (11.1)	30 (18.2), o	36.6 (7.8)[R]
Chio (2005) [10]	Italy	Cross-sectional	60 (63)	76.7	58 (12.3)	28 (25.2), o	24.6 (10.6)
Chio (2010) [28]	Italy	Cross-sectional	70 (67)	80.0	55 (13.3)	17 (9.3), o	29.2 (6.1)
Creemers (2015) [5]	The Netherlands	Longitudinal (12 months)	126 (66)	85.0	59 (12.5)	25 (n.r.), o*	31.8 (8.2)[R]
Galvin (2016) [29]	Ireland	Cross-sectional	81 (70)	71.6	55 (13.4)	n.r.	n.r.
Gauthier (2007) [6]	Italy	Longitudinal (9 months)	31 (71)	80.6	55 (11.3)	40 (31.5), o	28.7 (7.0)
Geng (2016) [30]	China	Cross-sectional	81 (68)	67.9	48 (14.5)	17.8 (14.9), o	36.5 (8.6)
Goldstein (1998) [20]	UK	Cross-sectional	19 (53)	100	60 (12.6)	34 (23.9), o	n.r.
Goldstein (2000) [19]	UK	Cross-sectional	19 (53)	100	60 (12.6)	34 (23.9), o	n.r.
Hecht (2003) [31]	Germany	Cross-sectional	37 (73)	81.1	57 (13.4)	25 (26.6), d	23.5 (9.1)
Jenkinson (2000) [24]	UK	Cross-sectional	415 (n.r.)	79.6	55 (13.1)	26 (29.5), o	25.9 (28.81)
Lillo (2012) [32]	Australia	Cross-sectional	140 (69)	90.0	61 (12.0)	36 (n.r.), o*	30.4 (9.7)[R]
Pagnini (2010) [22]	Italy	Cross-sectional	40 (70; 78)[2]	82.5	56 (12.3)	15 (n.r.), o	34.9 (7.8)[R]
Pagnini (2011) [33]	Italy	Cross-sectional	37 (62)	86.5	55 (11.4)	21 (4.2), o	27.8 (14.7)[R]
Pagnini (2012) [21]	Italy	Cross-sectional	40 (70; 78)[2]	82.5	56 (12.3)	15 (n.r.), o	34.9 (7.8)[R]
Pagnini (2016) [34]	Italy	Longitudinal (4 months)	114 (70)	82.3	57 (13.5)	32 (50.3), d	30.6 (9.9)
Qutub (2014) [23]	USA	Cross-sectional	50 (66)	n.r.	61 (n.r.)	37 (n.r.), o	34.10 (n.r)[R]
Rabkin (2000) [11]	USA	Cross-sectional	31 (61)	96.7	53 (12.0)	14 (n.r.), d	30.4 (4.7)
Rabkin (2009) [35]	USA	Longitudinal (monthly)[3]	71 (74)	63.0	57 (15.0)	n.r.	23.6 (7.8)[R]
Tramonti (2014) [36]	Italy	Longitudinal (6 months)	19 (68)	68.4	53 (11.6)	<6, d	18.2 (12.0)
Tramonti (2015) [37]	Italy	Cross-sectional	70 (69)	71.4	54 (11.5)	n.r.	n.r.
Tremolizzo (2016) [38]	Italy	Cross-sectional	84 (75)	78.0	n.r.	40 (37.5), n.r.	30.6 (9.0)[R]
Watermeyer (2015) [39]	UK	Cross-sectional	35 (72)	100	58 (10.5)	30 (14.3), o	34.1 (8.2)[R]

Abbreviations: ALSFRS, Amyotrophic Lateral Sclerosis Functioning Rating Scale [total score range 0- 40 (better functioning)]; d, time since diagnosis; n.r., not reported; o, time since disease onset; [R], Amyotrophic Lateral Sclerosis Functioning Rating Scale Revised [total score range 0- 48 (better functioning)]; sd, standard deviation; *, median.
[1] design of caregiver study [2] not consistently reported [3]only cross-sectional data with regard to burden was analyzed.

Table 2. Associations between caregiver factors and caregiver burden

	Factor[1]	Measure factor	Outcome caregiver burden	Bivariate association r	Bivariate analysis	Multivariate association β/OR (CI)	N	Ref
EMOTIONAL FUNCTIONING	Feelings of depression	BDI	ZBI-6 items	0.49*	P	-	31	11
		BDI	CBI	0.51***	P	-	82	38
		BDI-II	ZBI	0.43**	P	-	40	21
		BDI-II	ZBI	+n.r.***	R	-	50	23
		ZDS	CBI	0.55***	S	+n.r.*** (n.r.)	60	10
		ZDS	CBI	-	-	n.r.* (n.r.)	70	28
		ZDS	CBI	n.r.*	n.r.	-	31	6
		ZDS (t1)	CBI (t1)	n.r.*	n.r.	-	31	6
		HADS-Depression (t0-t3)	CSI (t0-t3)	-	-	NS	116	5
		HADS-Depression	ZBI	0.57***	P	NS	35	39
		DASS-Depression	ZBI-sv	-	-	NS^{or}	140	32
	Depression-somatic	BDI-II-Somatic	ZBI	0.84***	S	-	40	22
	Depression-psychological	BDI-II-Psychological	ZBI	0.57*	S	-	40	22
	Feelings of anxiety	HADS-Anxiety	ZBI	0.37*	P	NS	35	39
		HADS-Anxiety (t0-t3)	CSI (t0-t3)	-	-	0.19*** (0.086, 0.286)	116	5
		DASS-Anxiety	ZBI-sv	-		NS^{or}	140	32
		STAI-Trait	ZBI	0.36*	P	-	40	21
		STAI-Trait	ZBI-6 items	0.40 n.r.	P	-	31	11
	Distress	HADS-Total	ZBI	0.62***	R	-	33	27
		HADS-Total	ZBI	-	-	+n.r.** (n.r.)	81	29
		DASS-Stress	ZBI-sv	-	-	1.12^{or} * (0.86, 1.00)	140	32
	Mental health	SF-36-MCS	CSI	0.50***	n.r.	-	415	24
	Hopelessness	BHS	ZBI-6 items	NS	P	-	31	11
SOCIAL ENVIRONMENT	Social support	MQoL-Ss	ZBI	-0.73***	S	-	40	22
		5 point scale	ZBI	NS	P	-	31	11
		No. of friends/relatives seen	Strain Index	NS	S	-	19	19
		No. of close friends	Strain Index	NS	S	-	19	19
		No. of friends that can help	Strain Index	NS	S	-	19	19
		No. of substitute cgs	CBI	NS	S	-	60	10

Table 2. Continued

	Factor[1]	Measure factor	Outcome caregiver burden	Bivariate association r	Bivariate analysis	Multivariate association β/OR (CI)	N	Ref
SOCIAL ENVIRONMENT		Participating in support group	BSFC	NS	S	-	37	31
		Participating in support group	CBI	NS	S	-	60	10
		outside help received	ZBI	NS	R	-	50	23
		hours per week help	ZBI	NS	R	-	50	23
	Family functioning	FACES-Real cohesion	CBI	NS	S	-	19	36
		FACES-Real cohesion (t0)	CBI (t1)	-	-	0.53* (n.r.)	19	36
		FACES-Ideal cohesion	CBI	NS	S	-	19	36
		FACES-Real adaptability	CBI	NS	S	-	19	36
		FACES-Ideal adaptability	CBI	NS	S	-	19	36
		MIS	ZBI	-0.45**	P	NS	35	39
		MIS (change)	ISS-1	0.50*	n.r.	-	19	20
	Quality of care cg	numerical scale (t0-t3)	CSI (t0-t3)	-	-	-0.45*** (-0.672, -0.232)	116	5
DEMOGRAPHICS	Age	years	CBI	NS	S	-	60	10
		years	CBI	NS	n.r.	-	31	6
		years	CBI	0.24*	S	-	70	37
		years	ZBI	NS	P	-	35	39
		years	ZBI	-	-	NS	81	29
		years	ZBI	-n.r.**	R	-	50	23
		years	ZBI	-	-	0.19* (n.r.)	81	30
	Gender	male/female	CBI	NS	n.r.	-	31	6
		male/female	ZBI	-	-	NS	81	29
	Years married	years	ZBI	NS	P	-	35	39
	Relationship patient	Spouse/child/parent/..	ZBI	-	-	NS	81	29
	Living with patient	yes/no	ZBI	-	-	NS	81	29
	Household income	dollars	ZBI	NS	R	-	50	23
PERSONAL FACTORS	State of mindfulness	LMS	ZBI	-0.27**	P	-	140	34
		LMS (t1)	ZBI (t1)	-0.29*	P	-	140	34
		LMS (t0+t1)	ZBI (t0+t1)	-	-	-n.r.* (n.r.)	140	34
	Religiosity	RBI	ZBI-6 items	NS	P	-	31	11
		not-very religious	ZBI	NS	R	-	50	23
	Positive meaning in caring	FM-4 items	ZBI-6 items	0.49**	P	-	31	11
	Passive coping	UCL-PA (t0-t3)	CSI (t0-t3)	-		0.15* (0.015, 0.289)	116	5

Table 2. Continued

	Factor[1]	Measure factor	Outcome caregiver burden	Bivariate association r	Bivariate analysis	Multivariate association β/OR (CI)	N	Ref
PERSONAL FACTORS	Illness affects life areas	ISS-4	ISS-1	0.50*	n.r.	-	19	20
	Attribution style	Globality attribution measure	Strain Index	0.58**	S	-	19	19
	Control over reactions	Control over reactions measure	Strain Index	-n.r.*	S	-	19	19
PHYSICAL	Physical functioning	SF-36-PCS	CSI	0.28***	n.r.	-	415	24
	Physical fatigue	CFS-physical fatigue	ZBI-6 items	0.36 n.r.	P	-	31	11
CAREGIVING TIME	Time caring	hours per day	ZBI	NS	R	-	33	27
		hours per week	ZBI	-		n.r.* (n.r.)	81	29
		hours per day	ZBI	+n.r.*	R	-	50	23
	Time with patient	hours per day	ZBI	NS	R	-	50	23
	% time caring	% time of day	ZBI	NS	R	-	50	23

Abbreviations: BDI, Beck Depression Inventory; BHS, Beck Hopelessness Scale; BSFC, Burden Scale for Family Caregivers; CBI, Caregiver Burden Inventory; CFS-physical fatigue, Chalder Fatigue Scale, Physical Fatigue subscale; cgs, caregivers; CI, Confidence Interval; CSI, Caregiver Strain Index; DASS, Depression, Anxiety, Stress Scale; FACES, Family Adaptation and Cohesion Evaluation Scale; FM, Folkman's 4-item measure of finding positive meaning in caregiving; HADS, Hospital Anxiety and Depression Scale; ISS, Item Strain Scale; LMS, Langer Mindfulness Scale; MIS, Marital Intimacy Scale; MQoL-Ss, McGill Quality of Life social support subscale; n.r., not reported; no., number; NS, Not Significant; ^{or}, Odds Ratio; P, Pearson's product moment correlation; R, Univariate regression analysis; RBI, Religious Beliefs Inventory; S, Spearman's rank order correlation; SF-36, 36-item Short Form Health Survey Questionnaire; SF-36-MCS, 36-item Short Form Health Survey Questionnaire Mental Component; SF-36-PCS, 36-item Short Form Health Survey Questionnaire Physical Component; STAI, State-Trait Anxiety Inventory; UCL-PA; Utrecht Coping List Passive Approach subscale; ZBI, Zarit Burden Interview; ZBI-sv, Zarit Burden Interview-short version; ZDS, Zung Depression Scale.

[1]Factors and outcomes are measured at t0 unless mentioned otherwise.

* $p<0.05$; ** $p<0.01$; *** $p<0.001$

Table 3. Associations between patient factors and caregiver burden

	Factor[1]	Measure factor	Outcome caregiver burden	Bivariate association r	Bivariate analysis	Multivariate association β/OR (CI)	N	Ref
PHYSICAL HEALTH	Physical functioning	ALSFRS	CBI	-0.61***	S	-n.r.*** (n.r.)	60	10
		ALSFRS	CBI	-0.61***	n.r.	-	31	6
		ALSFRS (t1)	CBI (t1)	-0.64***	n.r.	-	31	6
		ALSFRS	CBI	-0.44**	S	-	70	37
		ALSFRS-R	CBI	-0.52***	P	-	84	38
		ALSFRS	BSFC	-0.47**	S	-	37	31
		ALSFRS-R	ZBI	-0.46*	S	-	40	22
		ALSFRS-R	ZBI	NS	R	-	33	27
		ALSFRS-R	ZBI	NS	S	-	40	25
		ALSFRS-R	ZBI	NS	R	-	50	23
		ALSFRS-R	ZBI-5 items	NS	P	-	71	35
		ALSFRS-R	CGBS	-	-	-0.58* (-1.1, -0.01)	86	26
		ALSFRS-R (t0-t3)	CSI (t0-t3)	-	-	-0.13*** (-0.170, -0.092)	116	5
	Bulbar function	ALSFRS-Bulbar	CBI	NS	n.r.	-	31	6
		ALSFRS-Bulbar	ZBI-sv	-	-	NS[or]	140	32
		ALSFRS-R-Bulbar	ZBI	NS	P	-	35	39
	Motor function	ALSFRS-R-Limb	ZBI	-0.66***	P	-0.51** (n.r.)	35	39
		ALSFRS-R-Upper limb	CBI	n.r.*	n.r.	-	31	6
		ALSFRS-Lower limb	CBI	n.r.*	n.r.	-	31	6
		ALSFRS-Fine motor	ZBI-sv	-	-	NS[or]	140	32
		ALSFRS-Gross motor	ZBI-sv	-	-	NS[or]	140	32
		ALSFRS-R Fine & Gross	ZBI	-	-	-0.52*** (n.r.)	81	30
	Respiratory function	ALSFRS-Respiration	CBI	NS	n.r.	-	31	6
		ALSFRS-Respiration	ZBI-sv	-	-	NS[or]	140	32
		ALSFRS-R-Respiration	ZBI	NS	P	-	35	39
		FVC	ZBI	-0.42**	P	-	40	21
		PCF	ZBI	-0.35*	P	-	40	21
	Disease progression	Progression index[2]	CBI	0.27*	P	-	84	38
	Physical health	SF-36-PCS	CSI	0.51***	n.r.	-	415	24
	Self care	CBI-R-Self care	ZBI	NS	S	-	40	25
	Everyday skills	CBI-R-Everyday skills	ZBI	0.41**	S	-	40	25
	Disease duration	years	CBI	-	-	n.r.* (n.r.)	60	10
		months	ZBI	NS	P	-	35	39
		months	CBI	NS	P	-	84	38

Table 3. Continued

	Factor[1]	Measure factor	Outcome caregiver burden	Bivariate association r	Bivariate analysis	Multivariate association β/OR (CI)	N	Ref
BEHAVIORAL IMPAIRMENTS	Behavioral impairments	FrSBe-Total	CBI	0.38***	P	+ n.r.* (n.r.)	70	28
		FrSBe-Total	ZBI	0.69***	P	0.69** (n.r.)	35	39
		CBI-R-Total	ZBI	0.66***	S	-	40	25
		FrSBe-Total (change)	ZBI	0.56*	R	-	33	27
		ALS-CBS-Behavior	CGBS	-0.76***	R	-0.69*** (-0.98, -0.41)	86	26
		ALS-CBS-Behavior	CBI	-0.22*	P	-n.r.* (n.r.)	84	38
	Apathy	FrSBe-Apathy	ZBI	0.63***	P	NS	35	39
		FrSBe-Apathy (change)	ZBI	0.39*	R	-	33	27
	Disinhibition	FrSBe-Disinhibition	CBI	NS	P	-	70	28
		FrSBe-Disinhibition	ZBI	0.51**	P	NS	35	39
		FrSBe-Disinhibition (change)	ZBI	0.53**	R	-	33	27
	Executive functioning	FrSBe-Executive dysfunction	CBI	0.44***	P	NS	70	28
		FrSBe-Executive dysfunction	ZBI	0.51**	P	NS	35	39
		FrSBe-Executive dysfunction (change)	ZBI	0.37*	R	-	33	27
		Battery of tests	ZBI	NS	P	-	35	39
	Behavior abnormalities	CBI-R-Abnormal behavior	ZBI-sv	-	-	1.44[or]** (1.13, 1.85)	140	32
		CBI-R-Abnormal behavior	ZBI	0.38*	S	-	40	25
	Eating habits	CBI-R-Eating habits	ZBI-sv	-	-	NS[or]	140	32
		CBI-R-Eating habits	ZBI	0.36*	S	-	40	25
	Stereotypic and motor behaviors	CBI-R-Stereotypical motor behavior	ZBI-sv	-	-	NS[or]	140	32
		CBI-R-Stereotypical motor behavior	ZBI	0.32*	S	-	40	25
	Motivation	CBI-R-Lack of motivation	ZBI-sv	-	-	NS[or]	140	32
		CBI-R-Lack of motivation	ZBI	0.43**	S	-	40	25
	Odd beliefs	CBI-R-Odd beliefs	ZBI	NS	S	-	40	25
COGNITIVE IMPAIRMENTS	Overall cognitive functioning	Neuropsychological tests	ZBI	NS	R	-	33	27
		MMSE	CBI	NS	P	-	84	38
		FAB	CBI	NS	P	-	84	38
		ALS-CBS-Cognition	CBI	NS	P	-	84	38
		ALS-CBS-Cognition	CGBS	-1.4*	R	-1.42* (-2.8, -0.05)	86	26
	Attention	ALS-CBS-Attention	CGBS	-0.25*	R	-	86	26
	Concentration	ALS-CBS-Concentration	CGBS	-0.25*	R	-	86	26
	Fluency	ALS-CBS-Fluency	CGBS	NS	R	-	86	26
	Memory/orientation	CBI-R Memory/orientation	ZBI	0.63***	S	-	40	25

Table 3. Continued

	Factor[1]	Measure factor	Outcome caregiver burden	Bivariate association r	Bivariate analysis	Multivariate association β/OR (CI)	N	Ref
	Executive functioning	WST	CBI	NS	P	-	84	38
	Social cognition	Battery of tests	ZBI	NS	P	-	35	39
EMOTIONAL FUNCTIONING	Feelings of depression	HADS-Depression (t0-t3)	CSI (t0-t3)	-	-	NS	116	5
		HADS-R-Depression	ZBI	NS	P	-	35	39
		BDI	CBI	NS	P	-	79	38
	Anxiety	HADS-R-Anxiety	ZBI	NS	P	-	35	39
	Emotional functioning	ALSAQ-40Se (t0-t3)	CSI (t0-t3)	-	-	0.02* (0.022, 0.042)	116	5
	Lability	ELQ	ZBI	NS	P	-	35	39
	Mental health	SF-36-MCS	CSI	0.28***	n.r.	-	415	24
	Mood	CBI-R-Mood	ZBI	0.38*	S	-	40	25
PERSONAL FACTORS	Existential wellbeing	MQol-Ewbs	ZBI	-0.60***	P	-	37	33
	Religion is source of strength	ALSSQoL-R statement (0-10)	ZBI	-0.43***	P	-	37	33
	Consider self as religious/ spiritual	ALSSQoL-R statement (0-10)	ZBI	-0.49***	P	-	37	33
	Self perceived as burden	SPBS	CBI	0.33*	S	NS	60	10
		SPBS	CBI	0.41*	n.r.	-	31	6
		SPBS (t1)	CBI (t1)	0.38*	n.r.	-	31	6
	Burden cg rated by patient	Visual analogue scale	ZBI-5 items	0.29*	P	-	71	35
	Active coping	UCL-AA (t0-t3)	CSI (t0-t3)	-	-	NS	116	5
	Age	years	ZBI	NS	R	-	33	27
DEMO-GRAPHICS		years	ZBI	0.35*	P	NS	35	39
		years	CSI (t0-t3)	-	-	NS	116	5
	Gender	male/female	ZBI	NS	R	-	33	27
		male/female	CGBS	-	-	8.1* (1.0, 15.2)	86	26
	Social support	MQoL-Ss	ZBI	-0.53**	P	-	40	21
SOCIAL ENVIRONMENT	Quality of care	n.r. (t0-t3)	CSI (t0-t3)	-	-	NS	116	5
	Family functioning	FACES-Ideal cohesion	CBI	-0.59**	S	-	19	36
	Reimbursement costs care	yes/no	ZBI	-	-	-0.19* (n.r.)	81	30

Abbreviations: ALSAQ-40Se, Amyotrophic Lateral Sclerosis Assessment Questionnaire 40-item subscale emotional functioning; ALS-CBS, Amyotrophic Lateral Sclerosis Cognitive-Behavioral Screen; ALSFRS, Amyotrophic Lateral Sclerosis Functional Rating Scale; ALSFRS-R; Amyotrophic Lateral Sclerosis Functional Rating Scale Revised; ALSSQoL-R, Amyotrophic Lateral Sclerosis Specific Quality of Life-Revised questionnaire; BDI, Beck Depression Inventory; BSFC, Burden Scale for Family Caregivers; CBI, Caregiver Burden Inventory; CBI-R, Cambridge Behavioural Inventory Revised; CGBS, Caregiver Burden Scale; CI, Confidence Interval; CSI, Caregiver Strain Index; ELQ,

Emotional Lability Questionnaire; FAB, Frontal Assessment Battery; FACES, Family Adaptation and Cohesion Evaluation Scale; FrSBe, Frontal Systems Behavior Scale; FVC, Forced Vital Capacity; HADS, Hospital Anxiety and Depression Scale; HADS-R, Hospital Anxiety and Depression Scale Revised; MMSE, Mini-Mental State Examination; MQoL-Ewbs, McGill Quality of Life existential wellbeing subscale; MQoL-Ss, McGill Quality of Life social support subscale; n.r., not reported; NS, Not Significant; OR, Odds Ratio; P, Pearson's product moment correlation; PCF, Peak Cough Flow; R, Univariate regression analysis; S; Spearman's rank order correlation; SF-36-MCS, 36-item Short Form Health Survey Questionnaire Mental Component; SF-36-PCS, 36-item Short Form Health Survey Questionnaire Physical Component; SPBS, Self-Perceived Burden Scale; UCL-AA, Utrecht Coping List Active Approach subscale; WST, Weigl's Sorting test; ZBI, Zarit Burden Interview; ZBI-sv, Zarit Burden Interview-short version.
[1]Factors and outcomes are measured at t0 unless mentioned otherwise [2] Calculated as ([48-ALSFRS-R]/disease duration in months.
* $p<0.05$; ** $p<0.01$; *** $p<0.001$

Table 4. Adapted GRADE table for narrative systematic reviews of prognostic studies

Potential factors	Participants (n)	No. of studies	Bivariate*				Multivariate				Grade factors					
			+	0	-	n.r.	+	0	-	n.r.	study limitations	inconsistency	indirectness	imprecision	publication bias	overall quality
Caregiver																
Feelings of depression	605	9	5	-	-	1	1	3	-	1	✓	✓	✓	×	✓	moderate
Feelings of anxiety	362	5	2	-	-	1	1	2	-	-	✓	✓	✓	×	✓	low
Distress	254	3	1	-	-	-	2	-	-	-	✓	✓	✓	×	✓	low
Social support	187	5	-	7	1	-	-	-	-	-	✓	✓	✓	×	✓	very low
Family functioning	73	3	-	4	2	-	1	1	-	-	✓	×	✓	×	✓	very low
Age	474	7	1	3	-	-	1	2	-	-	✓	✓	✓	×	✓	low
Patient																
Physical functioning	668	11	-	3	6	-	-	-	3	-	✓	✓	✓	×	✓	moderate
Bulbar function	206	3	-	2	-	-	-	1	-	-	✓	✓	✓	×	✓	low
Motor function	287	4	-	-	1	2	-	2	2	-	✓	✓	✓	×	✓	very low
Respiratory function	246	4	-	2	2	-	-	1	-	-	✓	✓	✓	×	✓	very low
Disease duration	179	3	-	2	-	-	-	-	-	1	✓	✓	✓	×	✓	very low
Behavioral impairments	348	6	6	-	-	-	4	-	-	-	✓	✓	✓	×	✓	high
Disinhibition	138	3	2	1	-	-	-	1	-	-	✓	✓	✓	×	✓	very low
Executive functioning	138	3	3	1	-	-	-	2	-	-	✓	✓	✓	×	✓	very low
Cognitive functioning	203	3	1	4	-	-	1	-	-	-	✓	✓	✓	×	✓	very low
Feelings of depression	230	3	-	2	-	-	-	1	-	-	✓	✓	✓	×	✓	low
Age	184	3	1	1	-	-	-	2	-	-	✓	✓	✓	×	✓	very low

For uni- and multivariate analyses: +, number of significant associations with a positive value; 0, number of non-significant associations; -, number of significant associations with a negative value; n.r., number of associations of which the direction was not reported. For GRADE factors: ✓, no serious limitations; ×, serious limitations. For overall quality of evidence: very low, low, moderate, high.

*Bivariate associations that are measured twice in one study on different measuring points are counted as one association.

was investigated in six studies. Patients' 'physical functioning' was most frequently studied (*n*=11). There was moderate quality of evidence for the relation between decreased physical functioning and higher caregiver burden. Very low quality of evidence was found for the association with higher caregiver burden and the factors 'limb function', 'respiratory function', 'executive functioning', 'cognitive functioning' and 'age'. Low evidence was found for 'bulbar function' and 'feelings of depression', and very low quality of evidence for 'disease durations' as factors not associated with caregiver burden.

Since each of the factors within the categories personal factors and social environment was studied in single or two studies, no synthesis of evidence could be performed.

Discussion

In our systematic review, we focused on both patient factors and caregiver factors in relation to burden in caregivers of ALS patients. Moderate to high quality of evidence was found for 'behavioral impairments' of the patient, 'physical functioning' of the patient and 'feelings of depression' of the caregiver as factors related to caregiver burden. These results indicate that there is a specific group of caregivers that is vulnerable to caregiver burden. For the relations between caregiver burden and the remaining caregiver and patient factors, the quality of evidence was low to very low and no general conclusions could be drawn.

We found high quality of evidence for the relation between caregiver burden and behavioral impairments of the patient. Behavioral impairments such as apathy or disinhibition occur in a substantial proportion of ALS patients and 5–15% of patients meet criteria for frontotemporal dementia (FTD), which is associated with more severe behavioral impairments.[46, 47] The findings of this review highlight the impact of behavioral impairments in patients on caregiver burden, whereas cognitive impairments in patients are less likely to result in caregiver burden. This underscores the relevance of the distinction between pure ALS, ALS with behavioral impairment (ALSbi), ALS with cognitive impairment (ALSci) and ALS with FTD (ALS-FTD).[48]

Moderate quality of evidence was found for the relation between caregiver burden and the level of physical functioning of the patient. Caregiver burden seems to increase parallel to the disease severity of the patient, which is in line with conclusions in other progressive neurological diseases.[49, 50] Low to very low quality of evidence was found for the relation between caregiver burden and factors measuring functioning in specific physical areas (e.g. respiratory function, motor function), indicating that burden seems to be related to the overall physical functioning but not to specific functions. The increase in burden may be the result of the fact that ALS leads to rapid decline in physical functioning, as this constantly requires physical and emotional adjustments from both

patient and caregiver.[51, 52] Furthermore, as the disease progresses, worsening of symptoms and physical concerns may lead to increased stress, worries, and burdens of caregivers, taking a toll on their time and energy for leisure activities and time to fulfill their own needs.[10, 22]

Moderate quality of evidence was found for the relation between caregiver burden and feelings of depression of the caregiver; in other words caregivers, who experience depressive symptoms, are more likely to experience high caregiver burden. This association between caregiver burden and depressive symptoms experienced by the caregiver is consistent with findings in other neurological diseases, such as dementia and stroke.[50, 53] Caregivers who experience feelings of depression may find it even more challenging to cope with the caregiving demands placed on them, which influences caregiver burden. Although research seems to indicate that caregiver burden and depression are distinct constructs,[54, 55] there might be some conceptual overlap between the measures of depressive symptoms and caregiver burden.[56] Questions related to depressive feelings are often included in burden measures (e.g. I feel emotionally drained due to caring for him/her. Caregiver Burden Inventory item 9; Do you feel tired and worn out? Caregiver Burden Scale item 1). However, in this review, we conceived caregiver burden and depression as two separate concepts because caregiver burden represents outcomes specific to the caregiving situation, while measurements of depression represent a more general outcome.

In previous systematic reviews, the suggestion was made that social support might be a protective factor for caregiver burden[12, 57] but this result could not be confirmed in our review. This difference might be attributed to the inclusion of both quantitative and qualitative studies. An alternative explanation could be that only specific subtypes of social support (i.e. emotional-, instrumental-, informational-, or appraisal support)[58] mitigate caregiver burden. For example, the benefits of receiving social support in caregiving (instrumental support) may be overestimated in ALS care, as taking over caregiving tasks is complicated, especially in later stages of the disease. Family members and friends are often not equipped to offer this specialized care to the patient.[4] Hence, relieving the burden of the caregiver by providing physical support in caregiving seems to be a difficult task for their social environment, while relieving caregiver burden with emotional support may be more feasible. However, it was impossible to make this differentiation in our review due to scarcity of research in this topic.

This systematic review offers insight into factors related to caregiver burden and guides the development of interventions aiming to reduce caregiver burden, but more additional research into factors related to caregiver burden is needed. Personal factors of ALS caregivers are possible modifiable factors but are currently understudied. Only 6 out of 25 of the studies included in this review paid attention to these factors. More knowledge about personal caregiver factors, such as feelings of competence in caregiving or self-efficacy, is needed since these personal factors seem to play a protective role in the development of burden in caregivers of patients with dementia.[59]

Strengths and limitations

This review was carried out in accordance with the PRISMA guidelines; the quality of the evidence was judged by assessing the risk of bias, and the GRADE approach was used, which are strengths of this review.

There were also some limitations of the review. First, it was not possible to perform a meta-analysis because of the heterogeneity of both the measures used to assess caregiver burden as well as the measures used to assess the associated factors. Second, the instruments used to assess caregiver burden represented different interpretations of the concept, caregiver burden. Therefore, we only included studies which assessed a total score on burden as this represents a general concept of burden. Others have suggested, however, that the use of multidimensional measures of caregiver burden might provide different information.[60] For the interpretation of results on caregiver burden, and the comparison of intervention effects, a gold standard for the measurement of burden in ALS caregivers would be preferable. Third, we only included full text, peer-reviewed published studies and therefore might have missed evidence about relationships between patient and caregiver factors and caregiver burden. Finally, the overwhelming majority of studies was cross-sectional and does not, therefore, allow any causal inferences between caregiver burden and factors. Longitudinal data is required to understand the temporal pattern of caregiver burden, its determinants and the optimal time to deliver an intervention to diminish caregiver burden.

Conclusion

This review presents the current knowledge on associations between both patient factors and caregiver factors which are related to caregiver burden in ALS caregivers. There is moderate to high quality of evidence for the relation between behavioral impairments of the patient and caregiver burden, physical functioning of the patient and caregiver burden, and feelings of depression of the caregiver him-/herself and caregiver burden. This is important knowledge in order to identify those caregivers who are at risk of caregiver burden and to inform the development of interventions focusing on diminishing burden in caregivers of ALS patients.

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APPENDIX 1. Prisma Checklist

Checklist Section/topic	#	Checklist item	Reported
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Yes
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Yes
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Yes
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Yes
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Yes
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Yes
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Yes
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Yes
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Yes
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Yes
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Yes
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Yes
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Yes
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	Yes
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Yes

APPENDIX 1. Continued

Checklist Section/topic	#	Checklist item	Reported on page #
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Yes
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Yes
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Yes
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group, (b) effect estimates and confidence intervals, ideally with a forest plot.	Yes
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Yes
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Yes
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Yes
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Yes
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Yes

APPENDIX 2. Literature search

Medline (via PubMed) search strategy d.d. 17 February 2015

Search ((((((((((((als[Title/Abstract]) OR amyotrophic lateral sclerosis[Title/Abstract]) OR mnd[Title/Abstract]) OR motor neuron disease[Title/Abstract]) OR motor neuron diseases[Title/Abstract]) OR motor neurone disease[Title/Abstract]) OR motor neurone diseases[Title/Abstract]) OR lou gehrig's disease[Title/Abstract]) OR lou gehrigs disease[Title/Abstract]) OR charcot disease[Title/Abstract]) OR amyotrophic lateral sclerosis[MeSH Terms])) AND ((caregiver[Title/Abstract]) OR caregivers[Title/Abstract]) OR care giver[Title/Abstract]) OR care givers[Title/Abstract]) OR caretaker[Title/Abstract]) OR caretakers[Title/Abstract]) OR carer[Title/Abstract]) OR carers[Title/Abstract]) OR partner[Title/Abstract]) OR partners[Title/Abstract]) OR next of kin[Title/Abstract]) OR family[Title/Abstract]) OR families[Title/Abstract]) OR parent[Title/Abstract]) OR parents[Title/Abstract]) OR spouse[Title/Abstract]) OR spouses[Title/Abstract]) OR husband[Title/Abstract]) OR husbands[Title/Abstract]) OR wife[Title/Abstract]) OR wives[Title/Abstract]) OR child[Title/Abstract]) OR children[Title/Abstract]) OR brother[Title/Abstract]) OR brothers[Title/Abstract]) OR sister[Title/Abstract]) OR sisters[Title/Abstract]) OR sibling[Title/Abstract]) OR siblings[Title/Abstract]) OR friend[Title/Abstract]) OR friends[Title/Abstract]) OR social support[Title/Abstract]) OR social network[Title/Abstract]) OR social networks[Title/Abstract]) OR significant other[Title/Abstract]) OR significant others[Title/Abstract]) OR relative[Title/Abstract]) OR relatives[Title/Abstract]) OR married person[Title/Abstract]) OR married persons[Title/Abstract]) OR spousal notification[Title/Abstract]) OR stepfamily[Title/Abstract]) OR stepfamilies[Title/Abstract]) OR support system[Title/Abstract]) OR support systems[Title/Abstract]) OR support system[Title/Abstract]) OR support systems[Title/Abstract]) OR neighbor[Title/Abstract]) OR neighbors[Title/Abstract]) OR neighbour[Title/Abstract]) OR neighbours[Title/Abstract]) OR family caregiver[MeSH Terms]) OR social support[MeSH Terms])) AND ((((((burden[Title/Abstract]) OR distress[Title/Abstract]) OR stress[Title/Abstract]) OR strain[Title/Abstract]) OR overload[Title/Abstract]) OR psychological stress[MeSH Terms])

EMBASE search strategy d.d. 17 February 2015

('caregiver':ab,ti OR 'caregivers':ab,ti OR 'care giver':ab,ti OR 'care givers':ab,ti OR 'caretaker':ab,ti OR 'caretakers':ab,ti OR 'carer':ab,ti OR 'carers':ab,ti OR 'partner':ab,ti OR 'partners':ab,ti OR 'next of kin':ab,ti OR 'family':ab,ti OR 'families':ab,ti OR 'parent':ab,ti OR 'parents':ab,ti OR 'spouse':ab,ti OR 'spouses':ab,ti OR 'husband':ab,ti OR 'husbands':ab,ti OR 'wife':ab,ti OR 'wives':ab,ti OR 'child':ab,ti OR 'children':ab,ti OR 'brother':ab,ti OR 'brothers':ab,ti OR 'sister':ab,ti OR 'sisters':ab,ti OR 'sibling':ab,ti OR 'siblings':ab,ti OR 'friend':ab,ti OR 'friends':ab,ti OR 'social support':ab,ti OR 'social network':ab,ti OR 'social networks':ab,ti OR 'significant other':ab,ti OR 'significant others':ab,ti OR 'relative':ab,ti OR 'relatives':ab,ti OR 'married person':ab,ti OR 'married persons':ab,ti OR 'spousal notification':ab,ti OR 'step family':ab,ti OR 'step families':ab,ti OR 'supportsystem':ab,ti OR 'supportsystems':ab,ti OR 'support system':ab,ti OR 'support systems':ab,ti OR 'neighbor':ab,ti OR 'neighbors':ab,ti OR 'neighbour':ab,ti OR 'neighbours':ab,ti OR 'caregiver'/exp) AND (als:ab,ti OR 'amyotrophic lateral sclerosis':ab,ti OR 'mnd':ab,ti OR 'motor neuron disease':ab,ti OR 'motor neuron diseases':ab,ti OR 'motor neurone disease':ab,ti OR 'motor neurone diseases':ab,ti OR 'lou gehrig/s disease':ab,ti OR 'lou gehrigs disease':ab,ti OR 'charcot disease':ab,ti OR 'amyotrophic lateral sclerosis'/exp) AND (burden:ab,ti OR strain:ab,ti OR distress:ab,ti OR stress:ab,ti OR overload:ab,ti OR 'caregiver burden'/exp) AND [embase]/lim AND ([dutch]/lim OR [english]/lim OR [german]/lim)

APPENDIX 3. Methodological Quality Assessment List

Item	Outcome Strategy	Criteria (positive=1, otherwise=0)
1.	*Internal validity:* Were the main outcome measures valid and reliable?	Positive, if the study tests the validity and reliability of the measurements used, or refers to other studies which have established the validity and reliability. validity and reliability.
2.	*Study participation:* Is the sample representative for the target group?	Positive, if specified how many persons were approached, how many persons participated, and a nonresponse analysis is done to compare participants and nonparticipants.
3.	*External validity:* Were the relevant patient characteristics specified (in- and exclusion criteria)?	Positive, if caregiver age, -gender, type of relationship with patient, time since patients' diagnosis and the physical functioning of the patient is reported.
4.	*Statistical validity:* Was the relationship between dependent and independent variables statistically valid?	Positive, if the relationship between a dependent and independent variable is tested for statistical significance.
5.	*Proportion sample size vs factors:* Was the sample size (n) adequate in relation to the number of factors (K)?	Positive, if univariate ratio [n:K] exceeds [20:1] and if multivariate ratio [n:K] exceeds [10:1].
6.	*Multicollinearity:* Was there a control for multicollinearity?	Positive, if specified that multicollinearity between variables has been tested.
7.	*Confounding bias:* Were potentially confounding variables controlled?	Positive, if specified that the design accounts for and analyses are corrected for confounders.
8.	*Reporting:* Are the main findings of the study clearly described?	Positive, if purpose is described, results are related to the purpose, statistical analyses are clearly reported, and data tables are explained in the results.

APPENDIX 4. GRADE factors

Item	GRADE factor	Criteria (no serious limitation = ✓, serious limitation=×)
1.	Study limitations	No serious limitation, if at least 75% of the studies are moderate- (total score 3-5) to high quality (total score 6-8) studies based on the Methodological Quality Assessment List.
2.	Inconsistency	No serious limitation, if the point of effect estimates are not on either side of the line of no effect.
3.	Indirectness	No serious limitation, if at least 75% of the studies used a study sample that fully represents the review question.
4.	Imprecision	No serious limitation, if 75% of the studies applied the rule of thumb: univariate ratio [n:K] exceeds [20:1] and if multivariate ratio [n:K] exceeds [10:1]. In which n represents the sample size and K the number of studied factors.
5.	Publication bias	No serious limitation, if the factor is investigated in 3 or more studies.

APPENDIX 5. Risk of bias

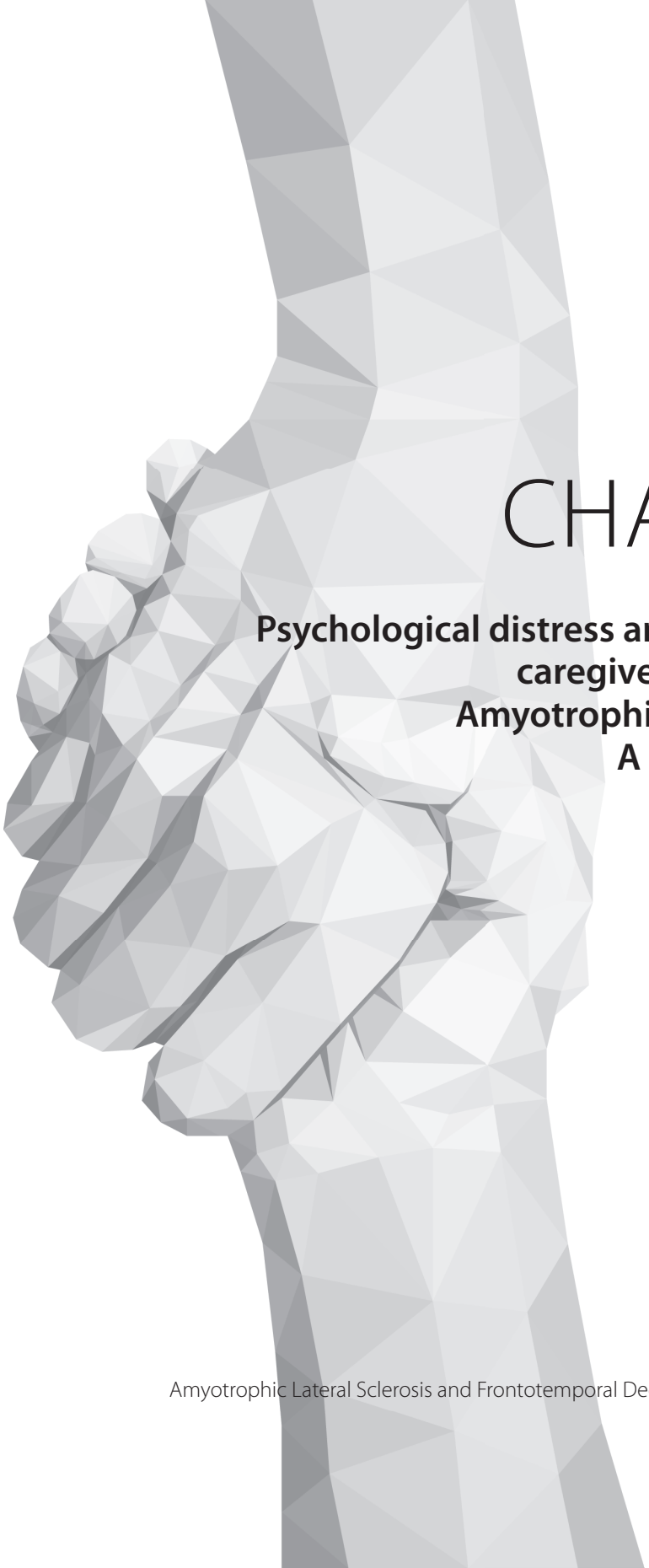
	Item [a,b]								
References	**1. Internal validity**	**2. Study participation**	**3. External validity**	**4. Statistical validity**	**5. Proportion sample size vs factors**	**6. Multi collinearity**	**7. Confounding bias**	**8. Reporting**	**Total**
Andrews (2016) [25]	1	0	0	1	0	NA	0	1	3
Bock (2016) [26]	1	0	0	1	0	1	1	1	5
Burke (2015) [27]	1	0	1	1	0	NA	0	1	4
Chio (2005) [10]	1	0	1	1	1	0	1	0	5
Chio (2010) [28]	1	0	1	1	1	0	1	0	5
Creemers (2015) [5]	1	0	1	1	1	0	1	1	6
Galvin (2016) [29]	1	0	0	1	1	0	0	0	3
Gauthier (2007) [6]	1	0	1	1	0	NA	0	0	3
Geng (2016) [30]	1	0	1	1	1	1	1	1	7
Goldstein (1998) [20]	0	1	1	1	0	NA	0	0	3
Goldstein (2000) [19]	0	1	1	1	0	NA	0	1	4
Hecht (2003) [31]	1	0	1	1	0	NA	0	1	4
Jenkinson (2000) [24]	1	0	0	1	1	NA	0	0	3
Lillo (2012) [32]	1	0	1	1	1	0	1	1	6
Pagnini (2010) [22]	1	0	1	1	0	NA	0	1	4
Pagnini (2011) [33]	1	0	1	1	0	NA	0	1	4
Pagnini (2012) [21]	1	0	1	1	0	NA	0	1	4
Pagnini (2016) [34]	1	0	1	1	1	0	1	1	6
Qutub (2014) [23]	1	0	0	1	0	NA	0	0	2
Rabkin (2000) [11]	0	0	1	1	0	NA	0	1	3
Rabkin (2009) [35]	0	1	0	1	1	NA	0	1	4
Tramonti (2014) [36]	1	0	1	1	0	0	1	1	5
Tramonti (2015) [37]	1	0	0	1	0	NA	0	1	3
Tremolizzo (2016) [38]	1	0	0	1	1	0	1	0	4
Watermeyer (2015) [39]	1	0	1	1	0	0	1	1	5

Notes. [a]0 = negative; 1 = positive; NA = not applicable [b]1. Positive if the study tests the validity and reliability of the outcome measures used, or refers to other studies which have established the validity and reliability; 2. Positive if specified how many persons were approached, how many persons participated, and a non-response analysis is done to compare participants and non-participants; 3.Positive if caregiver age, -gender, type of relationship with patient, and time since diagnosis or onset and physical functioning of the patient are specified; 4. Positive if the relationship between a dependent and independent variable is tested for statistical significance; 5. Positive if univariate ratio [n:K] exceeds [20:1] and if multivariate ratio [n:K] exceeds [10:1]; 6. Positive if specified that multicollinearity between variables has been tested; 7. Positive if specified that the design accounts for and analyses are corrected for confounders; 8. Positive, if purpose is described, results are related to the purpose, statistical analyses and results are clearly reported, and data tables are explained in the results.

APPENDIX 6. Caregiver burden instruments

Instrument	Description	Number of Items	Applied by studies in this review
Zarit Burden Interview (ZBI) [40]	This instrument is a measurement for the degree of caregiver burden. It covers areas mentioned by caregivers as problems including health, psychological wellbeing, finances, social life and relationship with the patient. Caregivers indicate how much discomfort each topic causes, choosing answer option from 'not at all' to extremely. The range of possible scores is 0-88, with a higher score indicating a greater level of burden.	22	11, 21-23, 25, 27, 29, 30, 32-35, 39 *, **, ***
Caregiver Burden Inventory (CBI) [41]	This instrument measures the impact of burden on caregivers. It is a multidimensional measure that permits distinction between five dimensions of burden (time dependence, developmental, physical, social and emotional). Scores for each item are evaluated using a 5-point scale ranging from 0 (not at all disruptive) to 4 (very disruptive). Total scores range from 0 (lowest level) to 96 (highest level).	24	6, 10, 28, 36-38
Caregiver Strain Index (CSI) [61]	This is a screening instrument for the detection of caregiver strain. The CSI contains 13 items, each scored on a dichotomous (yes/no) scale. CSI examines both subjective [e.g. feeling completely overwhelmed] and objective elements [e.g. there have been work adjustments] of caregiver strain. Total scores range from 0-13, higher scores reflect higher caregiver burden.	13	5, 24
Burden Scale for Family Caregivers (BSFC) [43]	This scale is a global measure of perceived burden. Its purpose is to cover all the relevant aspects which can contribute to caregiver burden. Every item is scored from 0 to 3 points (`quite correct', `correct on the whole', `correct in part', `not correct') resulting in a total score from 0 (lowest) to 84 (highest).	28	31
Caregiver Burden Scale (CGBS) [44]	This scale measures subjective burden and contains five indices; general strain, isolation, disappointment, emotional involvement and environment. Items are scored on a four point scale and total scores range from 22 (lowest) to 88 (highest).	22	26
Strain scale [45]	"I feel no strain because of the way my partner is nowadays" [1] to "I feel severe strain because of the way my partner is nowadays" [7]	1	19, 20

* Lillo, 2012 used the validated short 12 item version
** Rabkin, 2000 used 6 items of this instrument
*** Rabkin, 2009 used 5 items of this instrument



CHAPTER 3

Psychological distress and coping styles of caregivers of patients with Amyotrophic Lateral Sclerosis: A longitudinal study

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Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. 2019, 20(3-4), 235-241

Abstract

Objectives: To assess psychological distress levels over time in caregivers of patients in the early stage of Amyotrophic Lateral Sclerosis (ALS) and to investigate the association between caregivers' coping styles and psychological distress over time.

Methods: Fifty-four caregivers were followed in a Randomized Controlled Trial of patients in the early stage of ALS. Questionnaires were administered at baseline, 4, 7 and 10 months. Psychological distress was assessed using the Hospital Anxiety and Depression Scale (HADS) and task-, emotion-, and avoidance-oriented coping styles were identified with the short version of the Coping Inventory for Stressful Situations (CISS-21). Analyses were performed using linear mixed models.

Results: Caregivers' psychological distress increased by 0.24 points on the HADS per month (p = 0.01). An emotion-oriented coping style was positively associated with psychological distress in caregivers (b = 0.90, p < 0.01), but did not influence the development of psychological distress over time. The avoidance-oriented coping style and the task-oriented coping style were not significantly related to psychological distress.

Conclusion: Feelings of distress increase in ALS caregivers during the course of the disease of the patient. Emotion-oriented coping is related to psychological distress; however, emotional coping and distress might represent overlapping constructs. Focusing on one coping style in the care for ALS caregivers may be too simplistic for the complex situations they face, as it ignores the fact that people may require different coping strategies in different situations.

Introduction

Due to the rapid and progressive decline in muscle function in Amyotrophic Lateral Sclerosis (ALS), patients become increasingly dependent on others for the provision of care. Informal caregivers, mainly spouses, fulfill a major role in the care for patients with ALS.[1] As patients' disease progresses, caregivers can experience an increase in caregiver burden[2] and psychological distress.[3] Psychological distress can be defined as a discomforting, emotional state in response to a stressor.[4] Caregivers of patients with ALS are faced with all sorts of possible stressors during the disease course, such as the impact of the unfavorable prognosis, the lack of a curative treatment, the physical deterioration of the patient, cognitive or behavioral changes in the patient and accumulating caregiving demands.[5, 6] How caregivers respond to these stressors might influence the development of psychological distress.[7]

The general manner in which someone attempts to manage a stressor is called coping style[8], and coping styles are relatively stable over time within individuals.[9] In the literature, there is no consensus on the total number or nature of distinctions to describe coping styles.[8] Lazarus and Folkman[10] suggested there are two types of coping style: emotion-orientated- and task (or problem)- orientated coping. Emotion-oriented coping refers to emotional reactions directed toward oneself while the task-orientated coping is characterized by attempts to solve problems. Later, Endler and Parker[11] identified a third coping style: avoidance-oriented coping. Avoidance-oriented coping is characterized by attempts to avoid stressful situations either by engaging in other activities, or by interacting with others. The use of each coping style seems to have its own advantages and disadvantages, dependent on the circumstances.[8] In addition, the use of a specific coping style can be beneficial in the short term, but may lead to negative consequences in the long term.[12] For example, caregivers who use an avoidance coping style may deny that their partner is diagnosed with a fatal progressive disease, which decreases their feelings of stress on the short term. However, using this coping style on the long term may lead to poor adjustment as the condition of the patient will continue to progress. Requesting professional support and assisting aids may be needed which requires the use of problem focused coping strategies.

In previous coping research focused on caregivers of patients with traumatic brain injury and Alzheimer's disease, applying an emotion-oriented coping style was associated with more symptoms of burden and anxiety.[13, 14] Siciliano and colleagues[15] investigated coping in 96 ALS caregivers and concluded that only emotional-oriented coping was related to increased levels of depression, anxiety and burden. However, these studies are cross-sectional and do not provide information about the development of distress over time in relation to coping styles. More knowledge about the association between coping and distress over time could help to identify which caregivers are in need of support and could help to better tailor interventions to caregivers

at risk. Therefore, the objectives of the current study are to describe caregivers' psychological distress levels over time and to determine the association of caregivers' coping styles with psychological distress over time.

Methods

Participants and procedures

This longitudinal observational study was performed using the data of the FACTS-2-ALS trial in which patients with ALS and their caregivers were followed for 10 months.[16] Five outpatient rehabilitation clinics in The Netherlands participated, and caregivers were enrolled between October 2009 and November 2014.

Only informal caregivers, who were the partners of the patients, were included in the trial. Patients' inclusion criteria for the FACTS-2-ALS trial were: age between 18 and 80 years; life-expectancy of more than 1 year; predicted forced vital capacity of at least 80%; diagnosed at least one month with probable or definite ALS according to the revised El Escorial criteria[17] and having walking and cycling ability. Patients' exclusion criteria were: severe cognitive impairment, disabling co-morbidity, and psychological disorder, all assessed by the rehabilitation physician using the Cumulative Illness Rating Scale (CIRS).[18] Both patient and caregiver had to have sufficient mastery of the Dutch language.

In this study, patients were randomized to receive either care as usual, usual care plus aerobic exercise therapy, or usual care plus cognitive behavioral therapy for dyads. Patients who scored less than 8 on the Hospital Anxiety and Depression Scale (HADS) were not included in the cognitive behavioral therapy group. Since dyads in the cognitive behavioral therapy group received an intervention aimed at reducing stress, these couples were excluded from analysis. Care as usual for patients with ALS and their next of kin in The Netherlands consists of multidisciplinary care offered by specialized ALS care teams according to international guidelines.[19] These specialized ALS care include social workers and often also psychologists who offer psychosocial support. These psychosocial professionals provide mainly support to patients but also offer support to next of kin when psychosocial problems arise.

The Medical Ethics Committee of the University Medical Center Utrecht and all participating centers approved the study, which was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All participants provided informed consent.

Measurements and data collection

Caregivers

To measure psychological distress in caregivers, the HADS total score was used.[20] The questionnaire comprises 14 items about feelings of anxiety and depression over the past week. Items are scored on a 0 to 3 scale, with higher sum scores indicating a higher level of psychological distress. Cronbach's alpha was 0.91 at baseline in the caregivers' questionnaires, indicating good internal consistency. There are no strict cut-off criteria for the HADS.[21] We used a cut-off of 12 points or higher to identify psychologically distressed caregivers, based on a cut of for patients in outpatient rehabilitation.[22]

The short version of the Coping Inventory for Stressful Situations (CISS-21)[11, 23] was used to measure caregiver's preference in the use of each of the three coping styles: task-oriented coping, emotion-orientated coping, and avoidance-oriented coping. The questionnaire contains 21 statements on how to cope with a stressful situation. Each coping style is measured with seven statements structured on a 5-point Likert-scale from 'strongly disagree' to 'strongly agree'. Subscale scores range from 7 to 35, with higher scores indicating a preference for the use of a particular coping style. Cronbach's alpha of the subscales at baseline ranged from 0.76 to 0.84, indicating acceptable to good internal consistency.

Patients

Patients' disease severity was measured using the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R), a 12-item questionnaire with response categories ranging from 0 to 4. Lower scores indicate a higher level of disease severity.[24] Psychological distress was measured with the HADS, as in caregivers.

Data collection

Data were collected through questionnaires at baseline and after 4, 7 and 10 months. Demographic variables and the CISS-21 were self-administered at home. The ALSFRS-R and the HADS were administered by a rehabilitation physician at baseline and by a research assistant at 4, 7 and 10 months.

Statistical analysis

Participant characteristics were summarized using means, standard deviations, medians and interquartile ranges for continuous variables and proportions for categorical variables. Statistical analyses were performed using linear mixed models. Since there was some variation in the timing of the follow up measurements, we converted the moments of measurement into months after baseline based on the assessment date. To assess the relationship between each coping style at baseline and caregivers' psychological distress over time, models with and without the interaction between time and coping style were fitted. The factors time and coping were centered prior to the interaction analysis. In order to account for individual trajectories, we assessed the need for

a random intercept and slope in every model. A random intercept and random slope were only included if this improved the model fit based on the likelihood ratio test. Since longitudinal data on coping styles of the caregiver were available, the stability of coping was evaluated using linear mixed models. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.0.

Results

Number of participants and follow-up

A total of 64 caregiver-patient couples were included in the FACTS-2-ALS trial, 10 of whom were enrolled in the Cognitive Behavioral Therapy (CBT)-group. Therefore, data from 54 caregivers were included in the current study. At the 4, 7 and 10 months measurements, 47, 41 and 38 caregivers completed the questionnaires, respectively. Of the total of 16 caregivers who did not complete the last questionnaire, 5 dropped out due to the death of the patient, 1 caregiver dropped out due to feelings of burden, 1 caregiver died, 1 caregiver did not receive the questionnaire, and 8 caregivers did not report a reason for not filling in the questionnaires.

Demographics

Table 1 reports the descriptive characteristics for caregivers and the ALS patients for whom they provided care. Almost half of the caregivers were psychologically distressed at baseline (n = 23, 42.6%). Mean HADS total scores at baseline were 10.8 (SD 7.2) and 7.7 (SD 4.6) for caregivers and patients, respectively. On average, caregivers scored highest on the task-oriented coping style at baseline compared to the other coping styles. Eighty-nine percent of the caregivers indicated using all three coping styles to some degree and eleven percent reported a preference for only two different coping styles.

Course of psychological distress over time

Caregivers' psychological distress increased significantly over time, with 0.24 points on the HADS per month ($p = 0.01$), see Table 2. Including a random intercept and a random slope for time in this model resulted in a better fit of the model, indicating that the course of psychological distress differed between caregivers.

Coping in relation to distress

The stability of the preference for the use of each coping style was analyzed (see Table 3). Scores on emotion-oriented and avoidance-oriented coping did not change over time. The preference for the use of task-oriented coping style decreased over the study period ($b = -0.25$, $p = 0.003$).
The results of the analyses assessing the association of caregivers' coping styles with psychological distress over time are presented in Table 4. These results show that higher scores on the emotion-

oriented coping style subscale are associated with psychological distress in caregivers ($b = 0.90$, $p = 0.001$). The interaction between emotion-oriented coping style and time was not significant, indicating that the scores on the emotion-oriented coping subscale did not influence the development of distress over time. The task-oriented coping style ($p = 0.24$) and the avoidance-oriented coping style ($p = 0.63$) were not significantly associated with psychological distress in caregivers.

Table 1. Baseline characteristics

Caregivers (N=54)	
Age, years mean (SD)	58.7 (10.9)
Female, *n* (%)	38 (70.4)
Relationship status[1]	
Living together, *n* (%)	50 (94.3)
Living seperately, *n* (%)	3 (5.7)
Highest level of education[2]	
High school, *n* (%)	10 (19.2)
Vocational training, *n* (%)	19 (36.6)
College or university degree, *n* (%)	23 (44.2)
HADS total score, mean (SD)	10.8 (7.2)
Caregivers psychologically distressed, *n* (%)*	23 (42.6)
CISS: task-oriented coping style, mean (SD)	24.3 (5.3)
CISS: emotion-oriented coping style, mean (SD)	15.2 (5.0)
CISS: avoidance-oriented coping style, mean (SD)	18.7 (5.6)
Patients (N=54)	
Age, years mean (SD)	60.2 (9.7)
Female, *n* (%)	15 (27.8)
Time since diagnosis, months median (Q1-Q3)	3.3 (2.2 – 5.1)
ALSFRS-R, mean (SD)	42.5 (3.8)
HADS total score, mean (SD)	7.7 (4.6)

Abbreviations: N, number of caregivers or patients; SD, standard deviation; %, percentage; HADS, Hospital Anxiety and Depression Scale; CISS, Coping Inventory for Stressful Situations; Q1, first quartile; Q3, third quartile; ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised.
*Identified by HADS total score ≥ 12.
[1] One caregiver did not answer the question.[2] Two caregivers did not answer the question.

Table 2. Caregivers' psychological distress over time (N=54)

	***b* (95% CI)**	**SE *b***	***p*-value**
Intercept	10.61 (8.69 -12.54)	0.96	<0.001
Change per month	0.24 (0.06 – 0.43)	0.09	0.012

Random effects: random intercept and random slope.
Covariance structure: Autoregressive structure (1) Heterogeneous
Abbreviations: N, number of caregivers or patients; CI, confidence interval; SE, standard error.

Table 3. Coping styles of caregivers over time (N=54)

	***b* (95% CI)**	**SE *b***	***p*-value**
Emotion-oriented coping			
Intercept	15.38 (14.09 – 16.67)	0.64	<0.001
Change per month	-0.10 (-0.22 – 0.02)	0.06	0.110
Task oriented coping			
Intercept	24.11 (22.74 – -25.50)	0.69	<0.001
Change per month	-0.25 (-0.41 – -0.09)	0.07	0.003
Avoidance-oriented coping			
Intercept	18.59 (17.08 – 20.09)	0.75	<0.001
Change per month	-0.06 (-0.18 – 0.06)	0.06	0.314

Random effects: random intercept and random slope.
Covariance structure: Autoregressive structure (1) Heterogeneous
Abbreviations: N, number of caregivers or patients; CI, confidence interval; SE, standard error.

Table 4. Coping styles associated with caregivers' psychological distress over time (N=54)

	***b* (95% CI)**	**SE *b***	***p*-value**
Model 1*			
Intercept	10.75 (9.20– 12.30)	0.77	<0.001
Change per month	0.22 (0.30 – 0.41)	0.10	0.026
Change per point on Emotion-oriented coping	0.90 (0.64 – 1.17)	0.13	<0.001
Model 2*			
Intercept	10.75 (8.84–12.65)	0.95	<0.001
Change per month	0.24 (0.06 – 0.43)	0.34	0.012
Change per point on Task-oriented coping	-0.21 (-0.56 – 0.14)	0.17	0.237
Model 3*			
Intercept	10.63 (8.71–12.55)	0.96	<0.001
Change per month	0.24 (0.06 – 0.43)	0.34	0.012
Change per point on Avoidance-oriented coping	-0.08 (-0.42 – 0.25)	0.17	0.631

Random effects: random intercept and random slope.
Covariance structure: Autoregressive structure (1) Heterogeneous
Abbreviations: N, number of caregivers or patients; CI, confidence interval; SE, standard error.
*The interaction between time and coping style was not significant and did not improve the fit of the model.

Discussion

The levels of psychological distress increased in caregivers over the ten months of follow-up. Furthermore, our results indicate that caregivers with an emotion-oriented coping style experience higher levels of psychological distress, but this coping style does not influence the development of distress over time. No significant relations were found between use of task-oriented coping and avoidance-oriented coping and psychological distress. Moreover, this study suggests that there is variety in the development of distress between caregivers which emphasizes the need to monitor the levels of psychological distress in individual caregivers of patients with ALS.

Our results are in contrast to two previous longitudinal studies in ALS caregivers that reported no change in distress over time.[3, 25] This might be due to the fact that we included caregivers of patients who were diagnosed more recently (median of 3.3 months).[3, 25] The increase in levels of distress shortly after the diagnosis may be caused by changes in the perspective of the future and the confrontation with the consequences of the disease. This is comparable to research findings in caregivers of cancer patients, which shows that having a partner who has recently been diagnosed with a potentially life-threatening disease is associated with psychological distress.[26, 27]

The relationship between the use of an emotion-oriented coping style and caregivers' psychological distress was also found in studies in caregivers of patients with ALS[15], dependent older persons[28], and in healthy adults.[29] Emotion-oriented reactions such as emotional responses, self-preoccupation or fantasizing could possibly lead to emotional complaints, which could accumulate over time, resulting in psychological distress. Another explanation for the relation between emotional coping and distress might be related to the content of the items. Items of the Emotion-orientated scale of the CISS refer to self-blame, experiencing worry and feeling upset and seem to be contaminated with distress (e.g. 'Become very upset').[30] It is likely that overlap between the content of the items is responsible for the associations between the CISS Emotion-oriented scale and distress found in both the present study and in previous studies.

Similar to the findings of a cross-sectional study among caregivers of patients with ALS[15], the current study showed that task-oriented and avoidance-oriented coping styles were not related to psychological distress. In caregivers of patients with dementia, task-oriented coping was associated with a decrease in psychological distress.[31, 32] This protective effect of the task-oriented coping style was not, however, found in caregivers of patients with ALS. Furthermore, the preference for using the task-oriented coping style was found to decrease over time. Although we should interpret these results cautiously, this might be related to the rapidly progressing disability of the patient which constantly leads to new challenges that often cannot be solved. Continuing to use a task-oriented coping style might be difficult in these circumstances. In

addition, caregivers and patients are repeatedly informed that they are not able to influence the disease progression of ALS, which may diminish the use of a task-oriented coping style.

Another possible explanation for not finding a relationship between these coping styles and distress might be the way we measured coping. The CISS provides a general inventory of coping styles used. However, in order to manage the complex situation of caring for an ALS patient, a wide range of coping strategies might be needed, depending on the situation. Recent approaches have recognized the importance of situation-specific variations in coping. Being able to effectively modify one's coping strategies according to the demands of different stressful situations is called coping flexibility.[33] Coping flexibility seems to lead to more adaptive outcomes and improved well-being.[33] Focusing on one coping style in the care for these ALS caregivers may be too simplistic for the complex situations they face. Care professionals may support caregivers by focusing on situations that are related to feelings of distress. Coaching caregivers in applying different coping strategies in these different stressful situations might be beneficial for the wellbeing of these caregivers. However, further research is needed to investigate the applicability of coping flexibility in ALS caregivers.

Strengths and Limitations

A strength of our study was the longitudinal design and the inclusion of patients in the early stage of the disease, which provided insights into the development of distress in caregivers during the first months of the disease trajectory and into when supportive interventions may be needed.

This study has several limitations. Because we conducted a secondary analysis on data of a randomized controlled trial, the study population was limited to the in- and exclusion criteria used in the trial, which were primarily based on patients. Consequently, it may not be correct to fully generalize the findings in our study population to the entire population of caregivers of ALS patients. Furthermore, we could not use data from the 10 patient-caregiver couples of the CBT-group, in which caregivers and patients were randomized if patients had higher psychological distress levels. Since psychological distress levels in patients and caregivers are correlated[34], the psychological distress levels we found might be an underestimation of psychological distress in the population as a whole.

The small sample size allowed only a limited number of covariates in our analysis. Due to these limitations, future studies are required to test the generalizability of the results and to determine the role of other caregiver factors (e.g. self-efficacy and professional support received) and patient factors (e.g. disease severity and cognitive and behavioral changes) in relation to the development of distress in caregivers.

Conclusion

Caregivers of patients with ALS experience increasing levels of psychological distress in the first phase of the disease. Over 40 percent of the caregivers seem to be psychologically distressed. Therefore, we advocate the monitoring of caregivers' distress symptoms over time by the multidisciplinary ALS care team in order to identify when supportive interventions are needed. Emotional coping is related to increased levels of psychological distress, but did not influence the development of distress over time. However, emotional coping and distress seem to be overlapping constructs. Measuring coping styles in general and tailoring the support to this coping style, may not do justice to the complex situation of ALS caregivers. As caregivers are confronted with various stressful situations in which they might need to apply different coping strategies, more knowledge about coping flexibility is required.

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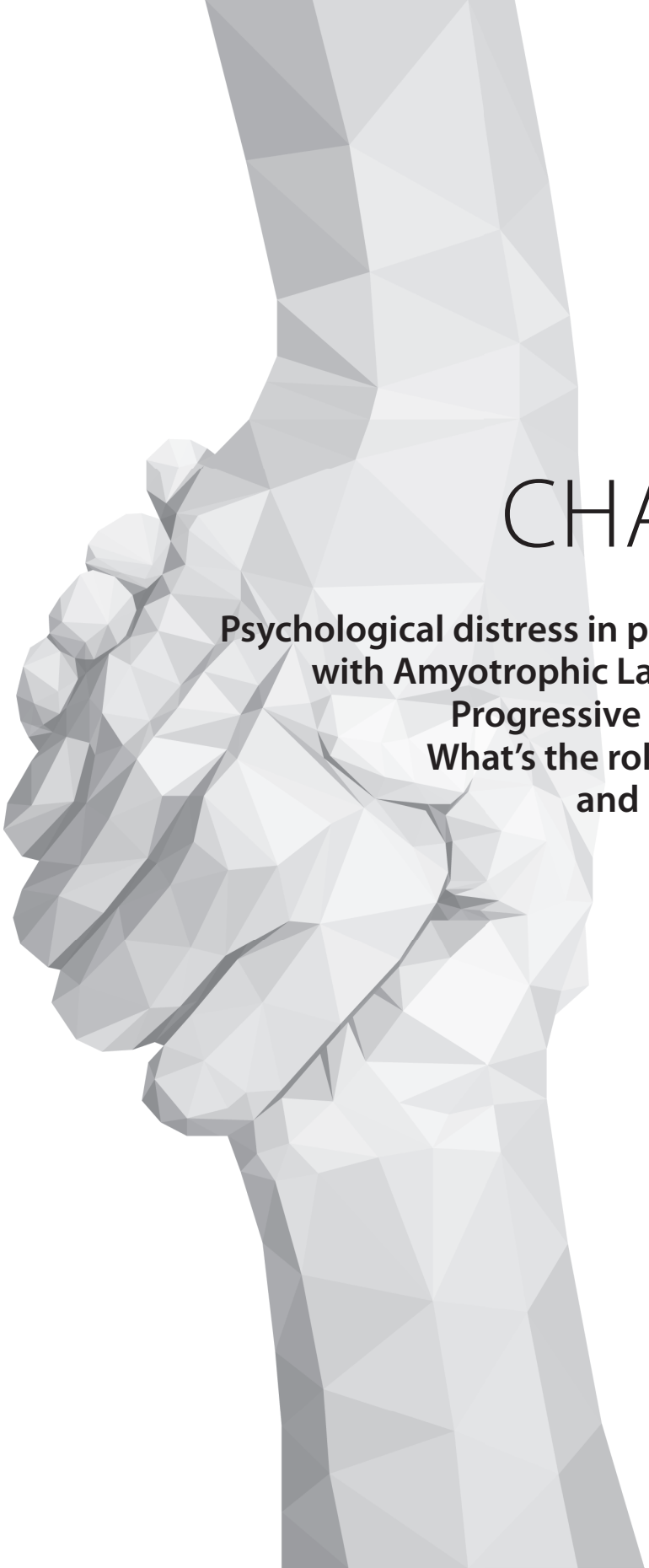

CHAPTER 4

Psychological distress in partners of patients with Amyotrophic Lateral Sclerosis and Progressive Muscular Atrophy: What's the role of care demands and perceived control?

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Under review

Abstract

Objective: Caregivers of Amyotrophic Lateral Sclerosis (ALS) and Progressive Muscular Atrophy (PMA) patients often experience psychological distress. Yet, it is unclear which factors explain the variance in psychological distress in caregivers. This study seeks to evaluate how care demands and perceived control over caregiving influence psychological distress in caregivers of patients with ALS and PMA using moderation and mediation analysis.

Methods: Data were collected as part of baseline measurement in a randomized controlled trial and 148 partners of patients with ALS or PMA were included. Psychological distress was assessed using the Hospital Anxiety and Depression Scale. Care demands were operationalized as physical functioning (Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised) and behavioral changes of the patient (Amyotrophic Lateral Sclerosis-Frontotemporal Dementia-Questionnaire). Perceived control over caregiving was assessed using 3 items adapted from the Job Content Questionnaire.

Results: Results showed that more behavioral changes in the patient and lower perceived control over caregiving were associated with higher levels of psychological distress in caregivers. These two factors accounted for 38% of the variance in psychological distress, after controlling for age. Patients' physical functioning was not significantly related to caregivers' psychological distress. No moderation or mediation effects were found of perceived control over caregiving on the relationship between demand and psychological distress.

Conclusion: Monitoring, psychoeducation and caregiver support with regard to the presence of behavioral changes in patients, seem to be important for improving the wellbeing of caregivers. Caregivers' perceived control might be a target for future interventions.

Introduction

Amyotrophic Lateral Sclerosis (ALS) and Progressive Muscular Atrophy (PMA) are progressive, neurodegenerative and fatal disorders. Patients suffer from progressive wasting and weakness of limb, bulbar and respiratory muscles, which lead to the inability to speak, respiratory failure and paralysis.[1] Approximately 50 % of ALS patients show cognitive or behavioral changes and 5-15 % fulfill the criteria of the diagnosis frontotemporal dementia (FTD).[2, 3] As a result, many informal caregivers have to deal not only with physical deterioration of the patient, but also with cognitive and behavioral impairments. Providing care for someone with ALS or PMA can be stressful; caregivers often experience feelings of distress (feelings of anxiety and depression), which seem to be related to the physical impairments and behavioral changes of the patient.[4] However, not all caregivers develop symptoms of psychological distress.

Several models that aim to explain the variance in psychological distress in caregivers have been studied in other patient populations.[5, 6] One of the models used is the demand-control model, which originates from occupational psychology.[7] This model has been applied to caregivers of elderly patients, stroke patients and heart failure patients.[8-10] According to this model, perceived control over caregiving may exert a moderating influence on the relation between the demands placed on the caregiver and psychological distress. This could explain the variance in psychological distress in caregivers. Other studies have, however, proved that feelings of control serve as a mediator between demands and psychological well-being in caregivers.[11, 12] This indicates that care demands directly influence feelings of control, which in turn affect the level of psychological distress. Gathering knowledge about these processes in ALS and PMA caregivers might provide valuable insights needed for the development of interventions.

The present study aims to investigate how care demands, operationalized as the physical functioning and behavioral changes of the patient, and perceived control over caregiving influence psychological distress in the caregivers of ALS and PMA patients using moderation and mediation analyses.

Methods

Design

The data used were the pre-randomization baseline data from a randomized controlled trial (RCT) which investigated the effectiveness of a psychosocial support program for caregivers of patients with ALS or PMA. The protocol of this rct has been reported elsewhere.[13] The protocol was approved by the Medical Ethics Committee of the University Medical Centre Utrecht (16-273-D) and all participants provided informed consent.

Procedure

Caregivers were recruited from July 2017 until March 2018 through a nationwide ALS/PMA database and through self-subscription via the website of the Dutch ALS Centre. Caregivers who were recruited through the database were contacted by telephone, informed about the study and inclusion criteria were checked. Eligible caregivers received the information folder and informed consent form at home. Caregivers who self-subscribed at the website received the information folder directly and were contacted by telephone to check the inclusion criteria. Caregivers who returned a signed informed consent, were included in the study and received an email inviting them to complete the online baseline questionnaire.

Participants

Caregivers met the following criteria: 1) the caregiver is the partner of the ALS or PMA patient; 2) the caregiver is 18 years or older; 3) the caregiver is proficient in Dutch in order to be able to fill in the questionnaires; 4) the caregiver has internet access; 5) the caregiver has the patient's consent to participate, as the caregiver answers questions about the patient.

Measures

Dependent variable, psychological distress

Psychological distress was measured using the Hospital Anxiety and Depression Scale (HADS)[14, 15], which consists of 14 items, seven measuring symptoms of anxiety and seven measuring symptoms of depression. Every item is scored on a 4-point scale, the total score ranging from 0–42. The total scale showed high internal consistency and test-retest reliability.[15]

Independent variable, demand

The demand variable was operationalized as the physical functioning of the patient and the behavioral changes of the patient. This was measured using two questionnaires that were completed by the caregivers:

1. Physical functioning of the patient

The physical functioning of ALS or PMA patients was assessed using the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALS-FRS-R).[16] The ALSFRS-R consists of 12 items to evaluate bulbar function, gross and fine motor function and respiratory function and each item is scored on a scale of 0 to 4. In this validated questionnaire, higher scores indicate better physical functioning.[16]

2. Behavioral changes of the patient

Behavioral changes in ALS or PMA patients were measured using the Amyotrophic Lateral Sclerosis- Frontotemporal Dementia-Questionnaire (ALS-FTD-Q)[17], which asks the caregiver to compare the patient's current behavior with his/her behavior 3 years ago. The validated questionnaire contains 25 items, the total score ranging from 0-100, with higher scores indicating more behavioral changes.[17]

Independent variable, perceived control

The perceived control variable was conceptualized as the caregivers' perceived control over caregiving. This was assessed using 3 items adapted from the Job Content Questionnaire[18] that are scored on a scale from 0 (completely disagree) to 3 (completely agree). The three items are: 1) "I feel that I have control over performing care tasks.", 2) "I feel that I have control over when I perform the care tasks." 3)"I feel that I have control over how I perform care tasks." The items show strong internal consistency (Cronbach's $\alpha = 0.93$).

Analyses

Descriptive statistics were used to explore the data. The relationships between age, gender, education and psychological distress were explored using correlations, Mann-Whitney U- and Kruskal Wallis tests. As these sociodemographic variables have been shown to be related to caregiver emotional outcomes[19, 20], they were considered as covariates. Factors that showed a significant relation with psychological distress were incorporated in the moderation and mediation analyses. Correlations were used to explore the relationships between the demand factors, perceived control and the outcome variable.

Moderation analyses

Two moderation models were tested, one for each type of demand (physical functioning and behavioral changes of the patient). To test each moderation model, a hierarchical multiple regression was performed. In the first step, the demographic factors that were significantly related to psychological distress were entered as independent variables. In the second step, demand and perceived control were entered as independent variables. The third step added a demand-multiplied-by-perceived control variable, to test for interaction. Independent variables (i.e. demand and perceived control) were centred prior to forming the interaction variable. Diagnostic plots of the residuals were evaluated to ensure that model assumptions were met.

Mediation analyses

The PROCESS tool was used to test the mediation models.[21] Unstandardized regression coefficients were calculated for each path in the mediation model. Path *a* represents the effect of X (physical functioning or behavioral changes in the patient) on the proposed mediator M (perceived control over caregiving). The second path, path *b,* represents the effect of M on Y (while statistically controlling for X). Path *c* represents the total effect of X on Y and path *c'* represents the direct effect of X on Y while partialling out the effect of M. The indirect effect of X on Y through M is equal to the product of *a* and *b* (*ab*). A bias-corrected 95% confidence interval is calculated for this indirect effect, based on 5,000 bootstrapped samples.[22] When zero is not included in a 95% confidence interval, it can be concluded that in 95% of the bootstrapped samples, the effect of demand on psychological distress is mediated through perceived control over caregiving.

Results

Participants

Table 1 presents the characteristics of the 148 participants who were included in the study. The majority of the caregivers were female (65%) whose male partners had been diagnosed with ALS. The mean time since diagnosis was approximately three years.

Factors relating to psychological distress

The correlations between the study variables showed that lower perceived control over caregiving and more behavioral changes in the patient were related to higher levels of caregivers' psychological distress (see table 2). The relationship between physical functioning of the patient and caregivers' psychological distress was not statistically significant. Age was the only demographic factor significantly related to psychological distress and was, therefore, included in the moderation and mediation models.

Moderation models

The first model included patients' physical functioning as demand, caregivers' perceived control over caregiving and caregivers' psychological distress. The overall model explained 18 percent of the variance of caregivers' psychological distress (F (4, 143) =7.82, $p< 0.001$) (see table 3). In this model, only perceived control over caregiving proved to be a significant predictor of caregivers' psychological distress. Neither patients' physical functioning nor the interaction between physical functioning and caregivers' perceived control were significantly related to caregivers' psychological distress.

Table 1. Caregiver and patient characteristics

Caregiver characteristics (*n*=148)	
Gender, *n* (%)	
Female	96 (64.9)
Male	52 (35.1)
Age in years, mean (SD)	61.55 (10.17)
Education level, *n* (%)	
Low	63 (42.6)
Medium	35 (23.6)
High	50 (33.8)
Baseline parameters, mean (SD)	
HADS [score range 0-42]	11.11 (7.14)
Perceived control over caregiving [score range 0-9]	6.34 (1.87)
Patient characteristics (*n*=148)	
Gender, *n* (%)	
Female	53 (35.8)
Male	95 (64.2)
Age in years, mean (SD), range	62.59 (9.9)
Diagnosis, *n* (%)	
ALS	106 (71.6)
PMA	42 (28.4)
Time since diagnosis in months, mean (SD), range	37.57 (40.8)
Onset area symptoms, *n* (%)	
Upper limb onset	56 (37.8)
Lower limb onset	55 (37.2)
Bulbar onset	32 (21.6)
Trunk onset	5 (3.4)
Baseline parameters, mean (SD), range	
ALS-FRS-R [score range 0-48]	31.36 (9.58)
ALS-FTD-Q [score range 0-100]	16.76 (12.88)

Abbreviations: ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; ALS-FTD-Q, Amyotrophic Lateral Sclerosis-Fronto Temporal Dementia-Questionnaire; HADS, Hospital Anxiety and Depression Scale
Educational level: low = did not complete secondary school-completed low level secondary school; medium = completed medium level secondary school; high = completed upper level secondary school and/or university degree

The second model included patients' behavioral changes as demand, caregivers' perceived control over caregiving and caregivers' psychological distress. The overall model explained 46 percent of the variance in caregivers' psychological distress (F (4, 143)=30.53, $p< 0.001$) (see table 4). Caregivers' perceived control over caregiving and patients' behavioral changes were both significant predictors of caregivers' psychological distress; lower perceived control and higher behavioral demand were related to higher levels of psychological distress. The interaction between patients' behavioral changes and caregivers' perceived control over caregiving did not add to the predictive power of the model beyond the main effects.

Table 2. Correlation coefficients of the study variables (*n*=148)

Variable	1	2	3
1. Psychological distress (HADS)	-		
2. Physical functioning patient (ALS-FRS-R)	-0.16		
3. Behavioral changes patient (ALS-FTD-Q)	0.60***	-0.16*	
4. Perceived control over caregiving (3-item scale)	-0.30***	0.13	-0.28**

Abbreviations: ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; ALS-FTD-Q, Amyotrophic Lateral Sclerosis-Fronto Temporal Dementia-Questionnaire; HADS, Hospital Anxiety and Depression Scale.
*p< 0.05; **p< 0.01, ***p< 0.001

Table 3. Hierarchical multiple regression analysis to predict caregiver distress (HADS total) using physical function of the patient (ALSFRS-R) and perceived control over caregiving

Step	Variable	*B*	*SE*	*β*	R^2	ΔR^2
1	Constant	23.18	3.48		.08**	
	Age	-.20**	.06	-.28		
2	Constant	31.77	3.96		.18***	.10***
	Age	-.19**	.05	-.27		
	Physical functioning patient	-0.06	.06	-.08		
	Perceived control over caregiving	-1.11**	.29	-.29		
3	Constant	32.66	4.08		.18***	.01
	Age	-.20***	.05	-.28		
	Physical functioning patient	-.06	.06	-.08		
	Perceived control over caregiving	-1.19***	.30	-.31		
	Physical functioning patient * Perceived control over caregiving	-.03	.03	-.07		

Abbreviations: ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; HADS, Hospital Anxiety and Depression Scale.
*p< 0.05; **p< 0.01, ***p< 0.001

Mediation models

The mediation analysis that included patients' physical functioning as demand, caregivers' perceived control over caregiving and caregivers' psychological distress showed only a significant direct effect of perceived control over caregiving on psychological distress (path *b* , B= -1.11, $p <$ 0.001) (see figure 1). The remaining paths (*a, c, c'*) and the indirect effect (*ab*) (B = -.03, CI = -.07, .01) were not significant.

The second mediation model included patients' behavioral changes as demand, caregivers' perceived control over caregiving and caregivers' psychological distress (see figure 2). A direct

Table 4. Hierarchical multiple regression analysis to predict caregiver distress (HADS total) using behavioral changes in the patient (ALS-FTD-Q) and perceived control over caregiving

Step	Variable	*B*	*SE*	*β*	R^2	ΔR^2
1	Constant	23.18	3.48		.08**	
	Age	-.20**	.06	-.28		
2	Constant	21.38	3.27		.46***	.38***
	Age	-.20	.04	-.28		
	Behavioral changes patient	.31***	.04	.56		
	Perceived control over caregiving	-.54*	.25	-.14		
3	Constant	21.33	3.27		.46***	.00
	Age	-.19***	.04	-.28		
	Behavioral changes patient	.31***	.04	.55		
	Perceived control over caregiving	-.57*	.25	-.15		
	Behavioral changes patient * Perceived control	-.02	.02	-.05		

Abbreviations: ALS FTD-Q, Amyotrophic Lateral Sclerosis-Fronto Temporal Dementia-Questionnaire HADS, Hospital Anxiety and Depression Scale.
*p< 0.05; **p< 0.01, ***p< 0.001

relation was found between patients' behavioral changes and psychological distress (path *c'*, B= .31, $p < 0.001$). In addition, patients' behavioral changes significantly predicted perceived control over caregiving (path *a*, B= -.04, $p < 0.001$) which in turn predicted psychological distress (path *b*, B= -.54, $p < 0.001$). However, the indirect effect was not significant (B = .02, CI = .00, .06).

Discussion

In this study there was support for the direct effects of patient's behavioral changes and caregivers' perceived control over caregiving on caregivers' psychological distress; when behavioral changes are present in the patient and when the caregiver experiences low levels of control over caregiving, caregivers' psychological distress is higher. Limitations in physical functioning of patients were not related to distress in caregivers. There was no moderation or mediation effect of caregivers' perceived control on the relation between demand (patients' physical impairments and behavioral changes) and caregivers' psychological distress.

Patients' behavioral changes emerged as the strongest predictor of caregivers' psychological distress in the models. A negative impact of behavioral changes such as apathy, disinhibition and abnormal behavior on caregivers' wellbeing, was also recognized in previous studies in ALS caregivers.[4, 23] The presence of behavioral changes is common in patients with ALS and PMA and becomes more frequent in more severe disease stages.[24, 25] However, patients and caregivers are not always informed that cognitive or behavioral changes can arise in these diseases.[26] Dealing

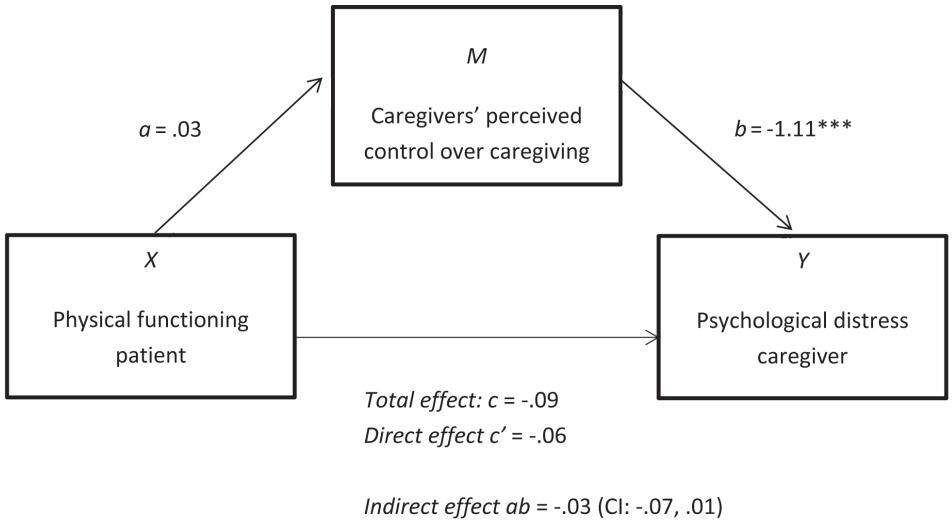

Figure 1. Mediation analysis 1, physical functioning patient, perceived control and distress

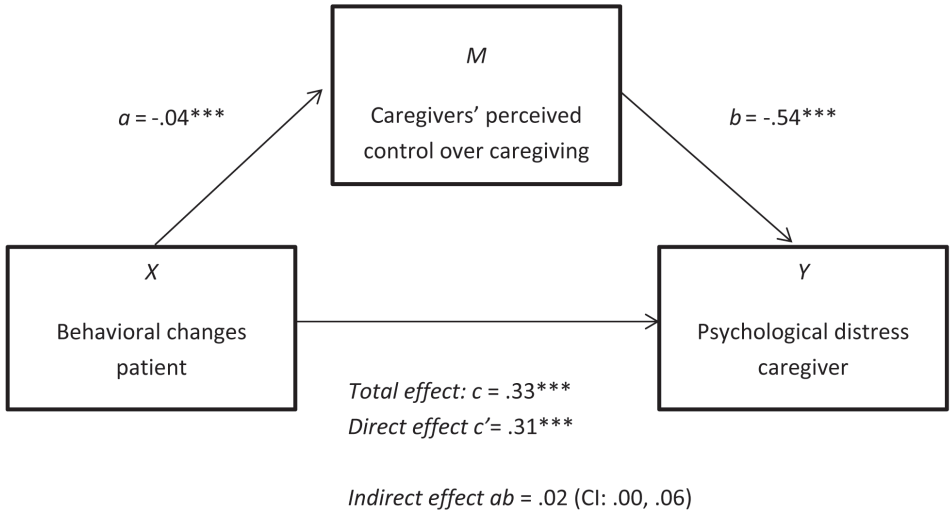

Figure 2. Mediation analysis 2, behavioral changes patient, perceived control and distress

with these behavioral changes without understanding the symptoms and their cause may be even more challenging for caregivers. Providing psychoeducation and supportive interventions for caregivers may be necessary to alleviate their feelings of distress. Interventions focussing on psychoeducation and teaching caregivers new coping strategies, aimed at dealing with behavioral changes in patients with dementia and traumatic brain injury, have shown promising results.[27-29]

In contrast to results of previous studies, patients' physical functioning was not related to caregivers' psychological distress. A number of studies have shown that caregivers of patients with ALS report higher levels of anxiety and depression in association with the physical impairments of the patients.[4, 30] These dissimilarities might be explained by differences in healthcare systems across countries; the Dutch healthcare system provides professional support at home which may relieve caregivers from the burden of physical care. Another possible explanation might reflect differences in the patient characteristics. The current study included caregivers of patients who were functioning well physically, while the mean time since diagnosis was over three years. Caregivers might become more distressed if the illness progresses more rapidly. The relatively slow disease progression in our sample might be explained by the inclusion of patients with PMA.

Higher caregivers' perceived control over caregiving was found to be a predictor of lower caregiver distress. This mirrors the findings of previous studies that investigated the effects of perceived control on distress and burden in stroke and heart failure patients.[8, 9] According to Rothbaum and colleagues[31], perceived control can be differentiated into primary and secondary control. Primary control describes the attempt to retain control by changing the environment (e.g., asking relatives to take over care tasks). Secondary control refers to changing one's own cognitions, beliefs, or replacing unattainable goals to adapt to the environment (e.g., deciding that an unreachable outcome is not desirable, after all). Previous research showed that interventions, focussed on influencing the environment (primary control) using psychoeducation (e.g. about the relation between environmental stimulation and behavioral disturbances) and environmental modifications (e.g. involving relatives), can help to increase the feeling of perceived control in caregivers.[32] Other studies have demonstrated that providing caregivers with cognitive skills and coping strategies (secondary control) to manage daily caregiving stressors can help increase their feeling of perceived control, self-efficacy or mastery.[33-35]

Results of the mediation and moderation models indicate that caregivers' perceived control does not influence or explain the relationship between demand and psychological distress. An explanation might be that the questions used to measure demand and control may not completely represent these constructs. The physical demand is assessed using the ALSFRS-R which provides an overall score of the patients' physical functioning. Equal scores on the ALSFRS-R can represent completely different disease expressions, which may lead to different experiences

of demand in caregivers. In addition, the questions used to measure perceived control may not cover the complete caregiver situation since they are limited to the execution of caregiver tasks. Caregivers might feel that they are fully capable of fulfilling care tasks but might feel that they do not have control over their lives in general.

Limitations

There are a few limitations to the present study, which should be acknowledged. First of all, a limitation is the cross-sectional design, which limits the conclusions that can be drawn from this data and prevents causal inferences being made. Secondly, a variety of factors that have been shown to influence caregivers' wellbeing were not taken into account in this study, such as social support[19], received care[36], and factors about the relationship of the caregiver and the patient.[37] Future studies should attempt to integrate these factors into theoretical models.

Conclusion

More behavioral changes in the patient and lower perceived control over caregiving are related to increased feelings of distress in caregivers of patients with ALS/PMA. It is recommended that the presence of behavioral changes in patients is monitored, and that psychoeducation and support for the caregivers, focussed on dealing with the behavioral changes, is provided. As perceived control might be a target for future interventions aimed at relieving feelings of distress in caregivers, further research into caregivers' perceived control over their lives as a whole is recommended.

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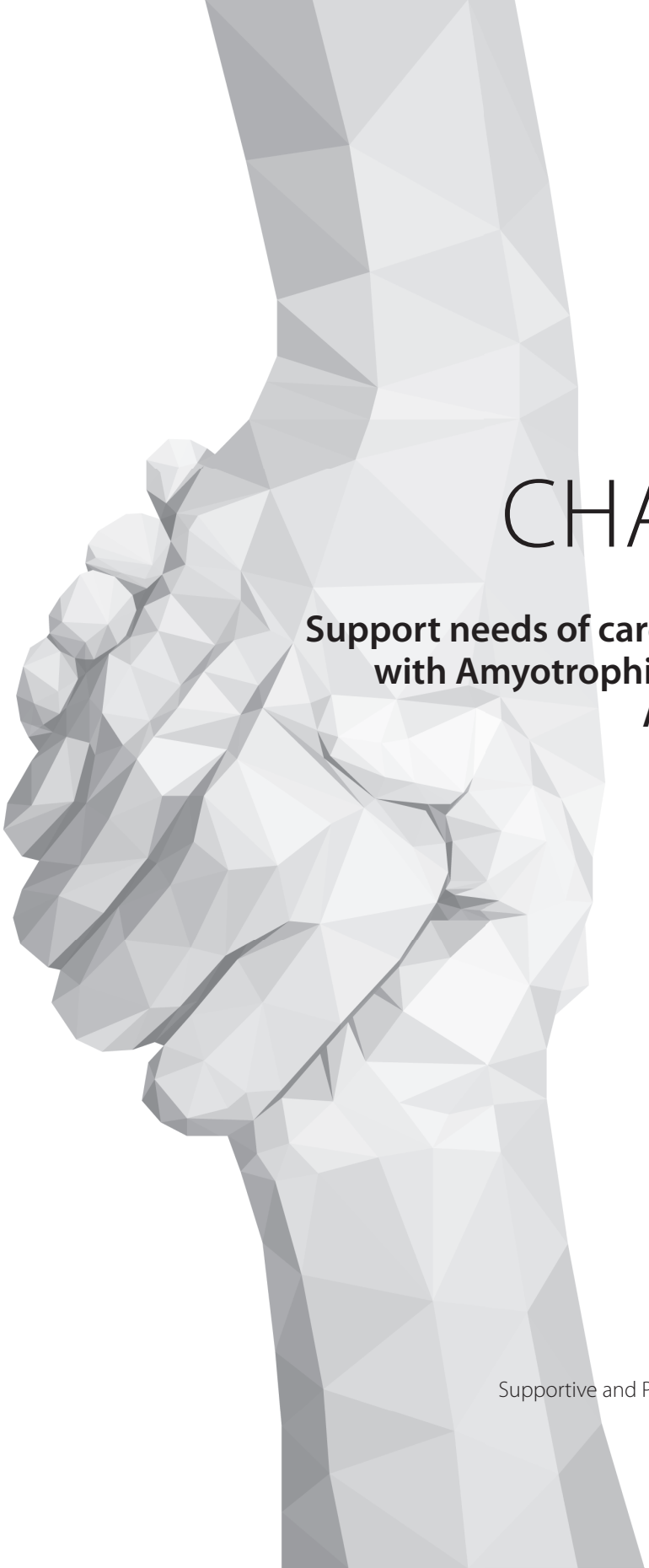
PART 2

Support needs of caregivers



CHAPTER 5

Support needs of caregivers of patients with Amyotrophic Lateral Sclerosis: A qualitative study

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Supportive and Palliative Care. 2019, 17(2), 195-201

Abstract

Objective: The aim of this study was to explore the support needs of Dutch informal caregivers of patients with Amyotrophic Lateral Sclerosis (ALS).

Methods: Individual semi-structured interviews were conducted with 21 caregivers of ALS patients. Audio-taped interviews were transcribed and data were analysed thematically.

Results: A total of four global support needs emerged: 'more personal time', 'assistance in applying for resources', 'counselling' and 'peer contact'. Despite their needs, caregivers are reluctant to apply for and accept support. They saw their own needs as secondary to the needs of the patients.

Conclusion: ALS seems to lead to an intensive caregiving situation with multiple needs emerging in a short period of time. This study offers targets for the development of supportive interventions. A proactive approach seems essential; acknowledging the importance of the role of the caregivers in the care process at an early stage, informing them about the risk of burden, monitoring their wellbeing and repeatedly offering support opportunities. Using e-health may help tailor interventions to the caregivers' support needs.

Introduction

Amyotrophic Lateral Sclerosis (ALS) is a fatal neurodegenerative disease that affects motor neurons, leading to the loss of all voluntary muscle function.[1] Although ALS is predominantly known for its physical deterioration, patients may also develop cognitive and behavioral symptoms including apathy, disinhibition and impairments in executive functioning.[2]

ALS is often described as a family illness, as it takes its toll not only on the patients, but also on their immediate social environment.[3] The majority of patients live at home and most of their care is provided by relatives, primarily partners. These informal caregivers spend increasing proportions of their time on caregiving activities, ranging from physical care to housekeeping tasks.[4] As a result, caregivers often experience physical symptoms, such as exhaustion, fatigue and sleeping problems.[5, 6] ALS not only puts a strain on caregivers in terms of time and energy, this burden also includes a significant psychological component. The close intertwinement of their life with that of the patient means that caregivers often feel that their own lives have been turned upside down.[7]

Previous research showed that caregivers who faced high care demands were more likely to experience poorer physical and mental health, particularly when they felt they lacked control over their caregiving tasks.[8, 9] Feelings of depression, psychological distress and quality of life of ALS caregivers worsen as the disease progresses and care demands increase.[10, 11] Although caregivers face high care demands, not all of them become distressed.[12] This would seem to indicate that the feelings of distress perceived by the caregivers are not only influenced by the demands made upon them, but also by other factors, such as control.

Despite the awareness of the decreased physical and mental health of caregivers and the importance of family support in comprehensive ALS patient care, evidence-based supportive interventions for caregivers are lacking.[13] A first step in the development of such interventions for ALS caregivers is to identify their support needs when caring for the patient. Qualitative research into this topic has previously been conducted in other countries. A study in the UK showed that caregivers reported a significant need for training in the manual handling and physical care of the patient.[14] A Swedish study reported the need for caregiver support groups to exchange experiences with caregiving, as well as a need for information and knowledge about the disease and care and a need for bereavement support.[15] In an Australian study, caregivers indicated they needed support to cope with experiences of loss and to adapt to changes in the care situation during the course of the disease.[7] Care needs seem to differ across countries and these differences may be caused by cultural differences and differences in the organization of health care and support services.[16]

In the Netherlands, care is organized along three disease phases: the diagnostic, rehabilitation and terminal phase.[17] The diagnostic phase is coordinated by a neurologist, the (palliative) rehabilitation phase by a rehabilitation physician and the terminal phase by a general practitioner. In the rehabilitation phase, care is provided by a multidisciplinary ALS care team and the social worker or psychologist of the team can also offer support to caregivers. Because of the cultural and healthcare differences, support needs of caregivers in The Netherlands may differ from those of caregivers in other countries. Therefore, the goal of this study was to explore the specific support needs of informal caregivers of patients with ALS in the Netherlands.

Methods

Study design

This study used a qualitative research design based on thematic analysis.[18] The study was submitted to the Medical Ethics Committee of the University Medical Center Utrecht in the Netherlands (15-272C), which deemed it exempt from review. Participation was voluntary and all participants signed an informed consent form prior to the interview. The reporting in this paper is in accordance with the Standards for Reporting Qualitative Research (SRQR) checklist.[19]

Participants

Informal caregivers of ALS patients were recruited via six specialized ALS care teams in hospitals or rehabilitation centres located in different regions of the Netherlands, using random sampling: any caregiver who was seen by the ALS care team could be included in the study. We asked rehabilitation physicians, psychologists and social workers to inform caregivers about our study by means of an information leaflet. Those interested were contacted and interviewed once. Twenty-one caregivers of patients with ALS were interviewed between February 2015 and August 2015. Table 1 presents the demographic characteristics of those interviewed, most of whom were women (n = 15) and co-resident partners of patients (n = 15). The majority (n = 14) experienced feelings of burden. Ten caregivers were providing care for patients with moderate disabilities, seven for patients with severe disabilities and three for patients who were very severely disabled. Twelve caregivers were interviewed within the first year after the patient's diagnosis.

Data collection

Interviews were conducted by the first author in a semi-structured format. The interviewer was not known to the participants prior to the start of the study. Based on a literature review, we formulated an interview guide including topics related to caregivers' need for support (Appendix 1).

The face-to-face interviews were held at a time and location of the participants' choosing (either in a rehabilitation centre or in their own home) and were conducted in a private setting. The patient was not present. The duration of the interviews ranged from 32 to 88 minutes. In order to gain insight into the severity of the patient's disabilities and the care demands placed on the caregiver, we asked participants to complete the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R).[20] This is a validated questionnaire-based scale that assesses the physical functioning of ALS patients, including gross motor tasks, fine motor tasks, bulbar functions and respiratory function. Higher scores denote better physical functioning. To facilitate clinical interpretation of the findings, the ALSFRS-R scores were categorized into four stages of severity: mild (37–48), moderate (25–36), severe (13–24) and very severe (0-12).[21] We also asked caregivers to complete the Caregiver Strain Index (CSI)[22], a questionnaire assessing strain as a result of caregiving. It consists of 13 items; total scores range from 0 to 13, with 7 or more indicating caregiver strain. It is an instrument with good construct validity and internal consistency, which can rapidly identify individuals with potential caregiving concerns.[22] After the interviews, respondent validation of the acquired data was performed by member checking.[23]

Data analysis

Interviews were audio-recorded, transcribed, anonymized and subsequently analysed by two researchers (JdW and JeM, research assistant, MSc Medical Anthropology). The process from data collection to analysis was iterative, as these processes were carried out simultaneously, so important themes that emerged from the analysis could be incorporated into subsequent interviews until saturation was reached.[24] Data saturation was achieved when no new themes were added during the last three interviews.

The first step of data analysis involved repeated reading of the transcripts to become familiar with the narratives and to annotate what was significant. Next, the texts were broken down into fragments based on content, and these fragments were labelled with codes using NVIVO 10.[25] This process was performed by the two researchers independently. Results of their coding were compared and discrepancies discussed in order to enhance the credibility of the results and to minimize interpretation bias. Once the coding of all interviews had been completed, codes were sorted in terms of similarities, and overarching themes and subthemes were identified based on the codes. Finally, a summary was written on each theme through a collaborative effort between the authors. Quotes were linked to the themes that expressed the essence of the content.

Table 1. Characteristics of caregivers

Characteristic	***n* = 21**
Group	
Current family caregiver	20
Bereaved family caregiver	1
Gender	
Female	15
Male	6
Relationship to patient	
Partner	15
Child	5
Sibling	1
Age	
70-79	3
60-69	4
50-59	6
40-49	2
30-39	4
20-29	2
Country of birth	
The Netherlands	20
Other	1
CSI score*	
0-6 (no burden)	6
7-13 (burden)	14
Time between diagnosis and interview	
< 1 year	12
1 – 2 years	3
2 – 3 years	2
3 – 4 years	3
> 5 years	1
ALS-FRS-R score patiënt*	*m* = 22.5 (*SD* = 9.2)
37-48 (mild physical disabilities)	-
25-36 (moderate physical disabilities)	10
12-24 (severe physical disabilities)	7
0-12 (very severe physical disabilities)	3

Abbreviations: ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; CSI, Caregiver Strain Index; *m*, Mean; *SD*, Standard Deviation
*These questionnaires were not completed by the bereaved caregiver.

Results

Support needs

Four major themes were identified with regard to the support needs of ALS caregivers: 'more personal time', 'assistance in applying for resources', 'counselling' and 'peer contact'. These, together with subthemes and quotations, are presented in table 2. The results are discussed by theme in the following section.

Having more personal time

Many caregivers sacrificed their working hours, leisure activities and social life to provide care. They adapted their lifestyle to the lifestyle of the patient, which resulted in a more restricted and inactive life (Quote 1 in Table 2). Providing care was often considered as burdensome, and having more personal time would offer some relief. Caregivers indicated that being able to leave the house and spend time on their own activities was important for maintaining their own wellbeing, and allowed them to divert their attention from ALS.

A significant strain, as well as an important barrier to having more personal time, was the fact that many caregivers were constantly on standby for their family member with ALS (Quote 2). This could partly be attributed to the continuous care tasks, even with paid home-care. But, an important factor here was the caregivers' concern that, in their absence, something could happen to the patient (e.g. falling, choking). Therefore, leaving the house was no longer a spontaneous activity and needed to be carefully coordinated, since alternative care had to be organized (Quote 3). Arranging this could be difficult since people in the caregivers' social network were often not equipped to take over care tasks.

A barrier to requesting (more) professional care was the lack of privacy inside the home due to the presence of healthcare professionals (Quote 4). One participant specifically chose to deliver the care by himself to maintain his privacy. Another option to create more personal time was respite care, in which professionals take over the responsibilities temporarily in order to relieve the caregiver. None of the caregivers had actually utilized respite care, although many had explored this possibility. Most were told that their care situation was too complex for respite care and that the required care needs could not be met (Quote 5). In one situation, respite care could only be provided at a nursing facility, which was rejected by the patient. Caregivers indicated that patients (strongly) preferred receiving care from their primary caregiver, making it complicated to get more personal time (Quote 6). To deal with the lack of personal time, some caregivers tried to focus on the temporary nature of care, as ALS implies a short life expectancy. This mind-set helped them persevere, but at the risk of continuously asking too much of themselves (Quote 7).

Table 2. Overview of categories and subthemes of caregiver needs

Categories of ALS caregiver needs	Subthemes	Quotes (Respondent number, gender, age)
More personal time	Restricted personal time due to caring	1. "Spare time, I don't really have that. That's just how it is when you provide care to someone who can't do anything. I would like to do a lot of things but I'm limited." (R17, male, 59)
		2. "Continuously being available. I find that very difficult (…) I feel like I'm only taking care of the basic things in life. There's no room for relaxation." (R3, female, 47)
		3. "People say 'You have to do some fun things, you have to think of yourself.' I understand that, but that's actually quite complicated." (R9, female, 35)
	Lack of privacy	4. "There are constantly people in our home; I don't have a private life anymore." (R4, male, 73)
	Respite care	5. "Respite care is too complicated in our family. I have been in contact about this topic several times. But it's only possible if … and that doesn't cover our situation." (R3, female, 47)
		6. "Yes, I would like it [respite care] very much. But I guess my father thinks otherwise." (R6, female, 38)
	Focus on temporariness	7. "I believe that she will live one more year. I can get through that year." (R2, male, 71)
Assistance in applying for resources	Aids	8. "It would be so helpful if the team [rehabilitation team] would apply for the devices for me. It would really help my frustration. I put a lot of time and effort in it [applying for devices] but I'm just not getting anywhere." (R11, female, 28)
	Health care reimbursement	9. "What drives me crazy is all the administration I have to deal with. It is one big mess. I think I can't cope with it anymore." (R20, female, 54)
		10. "It would be very nice if, when you're faced with such news [ALS diagnosis], you'd get a mentor, who says 'What do you need?' and 'These are the steps you have to go through'" (R9, female, 35)
Counselling	Expressing thoughts and feelings to an independent person	11. "Getting things off your chest, I like that. And I notice I tend to hide my grief. It's in those conversations that it comes out." (R8, female, 64)
		12. "What I needed was to talk to someone whom I didn't know, to whom I could tell my story, without having to feel guilty towards my husband." (R19, female, 67)
	Accepting diagnosis/dealing with emotions	13. "I feel powerless. Then I think why did he get ALS? Why? There's no answer." (R18, female, 67)
		14. "The deterioration [of the patient's condition] simply overcomes you. You just don't have the time or the space to process that your father is ill. (…) It's like getting on a speeding train." (R9, female, 25)

Table 2. Continued

Categories of ALS caregiver needs	Subthemes	Quotes (Respondent number, gender, age)
	Setting boundaries with regard to care	15. "I'm not assertive enough to set boundaries (…) but partly also because I think 'He's ill, he's dying! Should I say no all the time?' I know that I don't take enough care of myself (…). My time will come, so I'll leave it as it is. But in the meantime, it's destroying me." (R12, female, 29)
	Communication with patient	16. "That we [patient, caregiver and counsellor] can talk about the end of life. That [talking about the end of life] is also difficult for her. That's something that you keep postponing." (R4, male,73)
	Dealing with patient's behavior problems	17. "I'd like to receive tips on how I can deal with the situation [patient's apathy]. Do I need to push him? Or just leave things as they are?" (R6, female, 38)
Peer contact	Sharing experiences	18. "I would like to speak to someone who had also lost their mum or dad to ALS and, like me, is struggling with it. (…) Because I notice that in my environment, people just can't imagine what it's like." (R9, female, 25)
	Receiving information and tips	19. "An evening during which people can ask about problems others have encountered and how these problems were solved. I might hear things that I can use." (R11, female, 28)

Assistance in applying for resources

Participants expressed the need for professional help in managing the logistics of care provision. Most participants felt that applying for healthcare insurance reimbursement, home-care and aids, such as wheelchairs and communication technology, was a lengthy and convoluted process, leaving many frustrated (Quote 8). They had to go through different mandatory procedures before the required care could be provided (Quote 9). Consequently, some devices were delivered too late, as the condition had already progressed to a stage where the device was no longer useful.

For some caregivers it was not clear what kinds of devices were available and what type of professional home-care they could receive. Participants expressed a need for information on available support options. They would like to be supported in finding the right contacts and routes to get funding or aids (Quote 10).

Counselling

Some caregivers indicated that speaking to a professional in the absence of the patient would provide relief (Quote 11) and allow them to speak freely about their own concerns and needs without worrying how their statements might affect the person with ALS (Quote 12). Caregivers who discussed their issues with their social network often felt guilty when they talked negatively about the patient or the required care. They stated that counselling might help them cope with the diagnosis and their grief because they were struggling with acceptance and feelings of disbelief, anger, injustice, anxiety, sadness and guilt (Quote 13). In some cases a rapid progression of ALS complicated the situation for caregivers, as they felt they did not have enough time to come to terms with the disease (Quote 14).

Caregivers expressed the need for support in setting boundaries with regard to their personal needs and the amount and type of care they provided. Some participants indicated that setting boundaries caused feelings of guilt, as it meant they had to express their own needs in the face of someone suffering from a terminal illness (Quote 15). Looking back, burdened participants reflected that they had crossed their own boundaries without realizing it.

Some caregivers indicated that it was difficult to share their feelings with the patient or to discuss sensitive topics, such as death and euthanasia. They wanted support in addressing these topics and enhancing communication (Quote 16). Communication was particularly difficult when the person with ALS was unable to speak and had to make use of augmentative and alternative communication. Problems in communication were also provoked by the fact that some patients with ALS had become more withdrawn and less communicative since the diagnosis.

Caregivers noted various degrees of behavioral change in ALS patients since the onset of the disease, as a result of the psychological impact of ALS or as a consequence of cognitive problems caused by the disease. Some caregivers indicated they wanted support to help them cope with these behavioral changes. Two behaviors which stood out as being particularly problematic were apathy and demanding behavior. Apathetic patients behaved as if their life had already ended, and would not attempt any activities, rarely expressed themselves, and made little effort to make decisions. In these cases, caregivers were burdened with taking over decision-making, for example, with regard to care. Caregivers would like to be advised on ways to cope with apathy in patients (Quote 17). Demanding behavior constituted another difficult change, as caregivers felt that their family member with ALS made demands that were inconsiderate of others' needs. This led to participants struggling with feelings of not being in charge of their own life and of not being appreciated. Some participants mentioned that it was difficult to justify to themselves that they would like counselling support, worrying that this might be interpreted as an act of egocentrism.

Peer contact

Almost half the caregivers indicated that they would like to talk to other caregivers and share experiences, as these people would understand what they were going through in a way that their own social network could not (Quote 18). However, only a few participants actively searched for and contacted other caregivers. They did not know how to get in contact with them. Some were hesitant about such contacts, as they felt each situation was different and being confronted with patients in a more progressed state frightened them.

Receiving tips, information and advice was considered another major benefit of peer support. Caregivers expected that they could receive information from peers about how and when they should apply for care provision, which problems they might encounter and how they might solve them (Quote 19). Some searched the internet (e.g. blogs of other caregivers) to get information about others' experiences and about intimate topics that were difficult to discuss, such as having sex with a severely disabled ALS patient, but this was hard to find, and more information would be welcome. Some would be interested in joining a forum bringing together caregivers of ALS patients to answer each other's questions and share information. However, the majority indicated that they would be passive partakers and would only read the information.

Discussion

ALS caregivers reported a need for more personal time, assistance in applying for resources, counselling and peer contact. Despite these needs, caregivers were reluctant to apply for and accept support. Balancing their needs with their care responsibilities and the patients' needs was difficult for caregivers, and their priority were the needs and well-being of the patient.

Meeting the need for more personal time seems challenging for caregivers of ALS patients, as has also been recognized in other studies in ALS.[26] Caregivers reported that when they used paid home-care, they were confronted with reduced privacy. Additionally, caregivers experienced difficulties in handing over care to others, which often caused distress rather than relief. Handing over care tasks might be difficult in ALS care, due to the complexity of the tasks and the lack of experience with these task of others who are offering help.[27] However, these difficulties might also be partly attributed to the caregivers' own perceptions of their caregiving role and the expectations that patients have about care provision.[28] This appraisal process might lead to rejection of support and may result in caregivers feeling they have to be continuously available, which results in feelings of burden.[10] Research among dementia caregivers shows that caregivers often wait to seek help until they can no longer cope.[29]

Another stress-provoking issue for caregivers is the process of applying for resources, which is generally time-consuming and bureaucratic, whereas the need is often urgent. Unfortunately, caregivers and patients are not able to influence the speed and handling of this application process. Previous research found that the total number of perceived problems with health and social care services has a negative impact on the ALS caregivers' quality of life and strain.[30] Perceived problems of the application process may lead to a lack of balance between caregiving demands and feelings of control over caregiving tasks, and subsequently may lead to distress.[8]

Furthermore, caregivers reported a need for counselling on specific topics: setting boundaries, dealing with emotions and acceptance, dealing with behavior problems and communication. Setting boundaries with regard to care often leads to feelings of guilt[31] but seems to be crucial for the wellbeing of the caregiver, especially in the context of caring for a patient with a progressive disease. Interventions for caregivers that focus on topics such as information, dealing with emotions, coping skills and communication have proven to be effective among caregivers of patients with cancer and might be beneficial for ALS caregivers as well.[32] In addition, psycho-education about the patient's cognitive and behavioral decline might help the caregiver deal with behavior problems.[33] Despite these specific needs of caregivers, psychological support for caregivers is not yet a standardized part of ALS care in every multidisciplinary ALS care team.[17]

Another need among Dutch caregivers was reported to be peer support, having contact with other caregivers to share experiences and exchange helpful advice and information. This would be another potential target for intervention. Although some of the ALS care teams in the Netherlands organize peer support meetings for caregivers, caregivers find it difficult to attend these meetings, due to lack of time and the difficulties of handing over care to others. An online platform may enhance the accessibility and use of peer support groups.[34]

Contrary to other studies[35,36], Dutch caregivers in our study did not express a need for information about ALS or training in nursing skills.[35,37] This might be a result of cultural differences and differences in the organization of care.[16] In the Netherlands, specialized nursing care is predominantly provided by home-care professionals, which might be a reason why no need for training was reported by the Dutch caregivers. In addition, Internet access in the Netherlands is high and the ALS centre has an informative website, which may have resulted in the fact that Dutch caregivers were satisfied with the information provided.

Limitations

Our results need to be viewed in the context of the Dutch ALS care setting, in which specialized ALS care teams provide multidisciplinary care according to international guidelines.[38] This may limit the generalizability of our findings.

Implications

Suboptimal support for caregivers may have serious adverse consequences for the patients' wellbeing. Since ALS caregivers report being reluctant to ask for help despite their feelings of burden[36], a proactive and tailored approach is needed. Many factors can facilitate or hinder the use of a support service, such as the personal characteristics of the caregiver (e.g. perceived need, coping style), relational factors (e.g. relationship with the patient and support from the community) and the characteristics of the service itself (e.g. availability, quality, accessibility)[39]. Therefore, it seems essential for the healthcare professionals involved to acknowledge the importance of caregivers in the care of ALS patients at an early stage; inform caregivers about the risk of burden; monitor their wellbeing and repeatedly offer support opportunities (e.g. support organizations, respite care, psychosocial support). Since caregivers expressed the need for support but also reported lack of time, e-health can be an option to provide support at home in a less time-consuming manner. The majority of caregivers are known to use devices such as tablet computers or laptops on a daily basis and caregivers are open to technology-assisted care.[40] E-health may enable online psychological support, online contacts with peers and online information about applying for aids.[41]

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Appendix

APPENDIX 1. Interview guide

Can you tell me about yourself, what does a typical day look like for you?

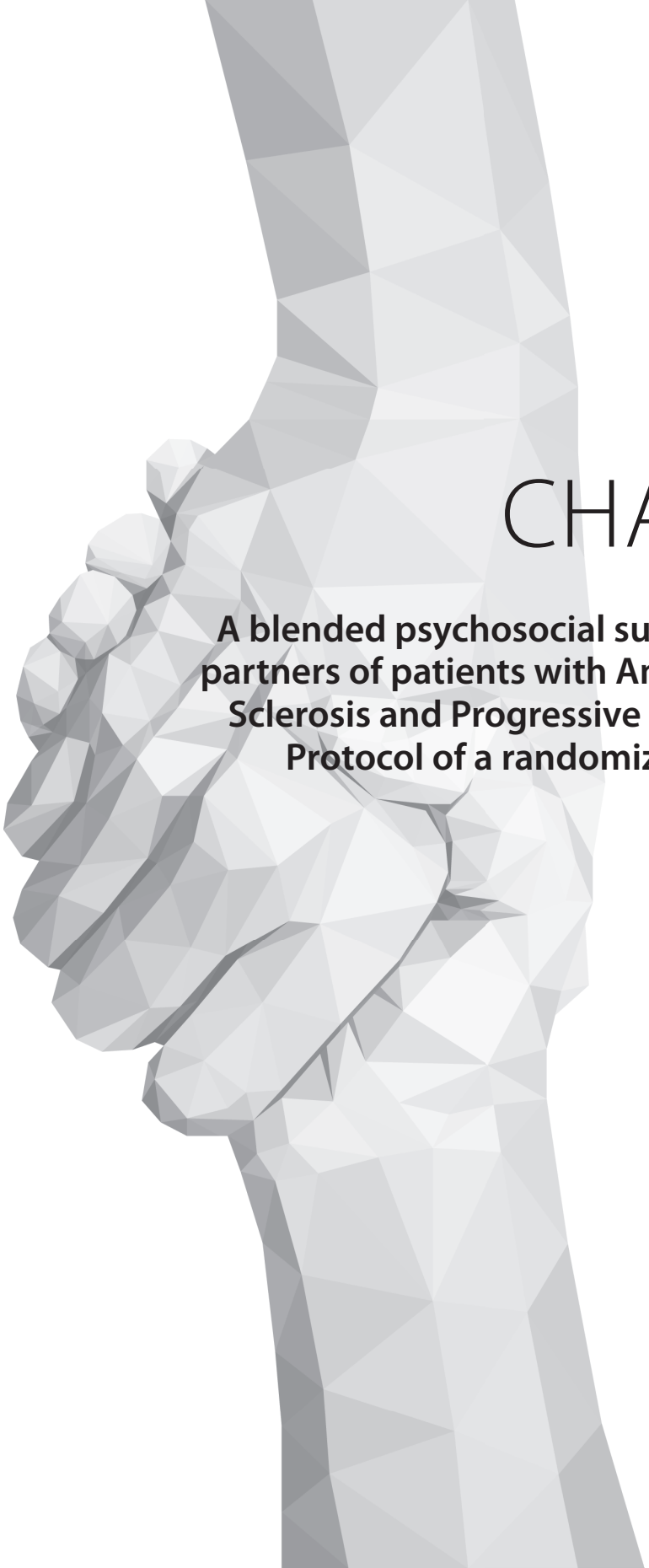
How do you feel about being a caregiver?

Do you feel a need for support in dealing with the caregiving situation?

- What do you need help with?
- What kind of support do you need?
- What would help you feel more capable of providing care?
- Do you have a need for more information about ALS? About what topics would you like more information?
- Would you like to have more contact with peers? Have you tried to make contact with peers?

PART 3

A blended support program: ALS caregiver support



CHAPTER 6

A blended psychosocial support program for partners of patients with Amyotrophic Lateral Sclerosis and Progressive Muscular Atrophy: Protocol of a randomized controlled trial

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BMC Psychology. 2018, 6(1), 20

Abstract

Background: Informal caregivers of patients with Amyotrophic Lateral Sclerosis (ALS) or Progressive Muscular Atrophy (PMA) face stressful demands due to severe impairments and prospect of early death of the patients they care for. Caregivers often experience feelings of psychological distress and caregiver burden, but supportive interventions are lacking. The objective of this study is to investigate the effectiveness of a psychosocial support program aimed at enhancing feelings of control over caregiving tasks and reducing psychological distress. This support program is based on an existing program for adult partners of people with cancer and is adapted to meet the needs of ALS caregivers.

Methods: This study is a randomized controlled trial using a wait-list control design. One hundred and forty caregiver-patient dyads, recruited from a Nationwide database and through the website of the Dutch ALS Center, will be either randomized to a support program or a wait-list control group. The blended intervention is based on Acceptance and Commitment Therapy and consists of 1 face-to-face contact, 6 online guided modules and 1 telephone contact. The intervention can be worked through in 8 weeks. The effectiveness and the participants' satisfaction with the intervention will be evaluated using a mixed method design. Caregivers and patients will be asked to fill in questionnaires on 4 occasions during the study: baseline, 3 months, 6 months and 9 months. The main study outcome is the psychological distress of the caregiver assessed with the Hospital Anxiety and Depression Scale. Secondary outcomes are caregiver burden, caregiver quality of life, quality of life of the patient and psychological distress of the patient. Group differences in primary and secondary outcomes at 6 months will be compared with linear mixed model analysis. In a subgroup of caregivers we will explore experiences with the support program through semi-structured interviews. Usage of the online modules will be logged.

Discussion: The study will provide insights into the effectiveness of a blended psychosocial support program on psychological distress of caregivers of patients with ALS or PMA, as well as into indirect relations with patients' wellbeing.

Background

Informal caregivers, usually the patient's partner, are key figures in Amyotrophic Lateral Sclerosis (ALS) and Progressive Muscular Atrophy (PMA) care. They provide the majority of support to patients and are often the primary caregivers. ALS and PMA are fatal motor neuron diseases, ALS affecting both upper and lower motor neurons while PMA only affects lower motor neurons. Informal caregivers of patients with ALS or PMA face stressful demands due to the prospect of an early death and severe impairments of the patient. Patients experience a progressive decline of muscle strength resulting in paralysis, difficulty with speech and swallowing, possible cognitive and behavioral problems and ultimately, respiratory failure leading to death.[1-3] Patients become increasingly impaired and the amount of care that is needed accumulates.[4]

Since PMA is a rare subtype of motor neuron disease, research studies on PMA caregivers are limited. However, PMA shows substantial overlap with ALS and is considered to be a form of ALS[5]; PMA caregivers are, therefore, likely to struggle with the same issues as ALS caregivers. The wellbeing of ALS caregivers has been studied more intensively and shows that as the disease progresses, ALS caregivers experience heightened feelings of psychological distress and burden[6-8], which results in a diminished quality of life.[9] The wellbeing of ALS-caregivers is critical because a high level of burden might predict a breakdown in care, leading to earlier placement of the patient in a care-home or hospice.[10] Therefore, improving the psychological health of the caregivers may not only improve their quality of life but also that of the patient.

Previous research has shown that psychological distress and feelings of burden of ALS caregivers are associated with disease characteristics of the patient (i.e. physical and behavioral problems) but also with characteristics of the caregivers themselves, such as their coping style or whether they find positive meaning in caregiving.[7, 9, 11-15] As the disease progresses, psychological and physical demands on the ALS caregiver increase. Patients become increasingly reliant on their caregiver, and caregivers have to take over responsibilities from the patient. Handling all these responsibilities, accepting a loved one's illness and accepting the loss of the patient in the near future are examples of issues ALS caregivers struggle with.[16]

ALS and PMA caregivers are faced with situations, yet may lack the relevant knowledge and skills, such as communicating about the disease and death, dealing with the patients' behavioral changes, dealing with their own emotions or expressing their own boundaries.[17] Consequently, caregivers may not feel competent or in control with respect to their caregiving tasks, while the demands increase. From previous studies we know that a combination of high demands and feelings of insufficient control over caregiving is associated with poorer physical and psychological health outcomes of caregivers.[18, 19] Previous studies have indicated that there is a need for psychosocial interventions for caregivers, but such interventions are still lacking.[6, 20, 21]

Acceptance and Commitment Therapy (ACT) is a form of cognitive behavioral therapy that encourages individuals to accept unwanted private events which are out of personal control (such as thoughts, feelings and memories) and to identify important values in life in order to engage in committed action to pursue these values.[22] The acceptance component in ACT makes this therapy valuable in contexts with circumstances that cannot be changed[23, 24], for instance, receiving a diagnose of ALS or PMA. The values component supports caregivers to undertake action that is personally meaningful. This can assist them in adjusting to their situation, in moving on in life and in enhancing their psychological wellbeing.[23] Applying acceptance strategies and living up to personal values requires a different way of responding to situations and may increase the feeling of control.[25]

ACT has proven to be effective in decreasing feelings of psychological distress in various target groups, including caregivers of other patient populations.[26-28] Recently, ACT has also been proved to be effective when delivered via the Internet.[28, 29] Since ALS and PMA caregivers are often preoccupied with the care for their home-bound patient, receiving care in a more accessible and time efficient manner may offer opportunities.

In this study, we will investigate the effect of a blended support program in which face-to-face contact and e-health will be combined. The support program is based on Acceptance and Commitment principles and focuses particularly on the needs of ALS and PMA caregivers. This support program aims to diminish caregivers' psychological distress by increasing their feelings of control in fulfilling the caregiving tasks for patients with ALS or PMA.

Methods

The described protocol (Version 6, dated 27-07-2017) has been developed according to the Standard Protocol Items Recommendations for Interventional Trials (SPIRIT) and the Template for Intervention Description and Replication (TIDIER).[30, 31]

Design

This study is a Randomized Controlled Trial (RCT) in which caregiver-patient dyads will be randomly allocated to one of two groups:

1. Intervention group (support program during 8-12 weeks).
2. Wait-list control group, receiving care as usual (6-month monitoring preceding the support program).

This design enables us to investigate whether offering a support program in addition to usual care improves the wellbeing of caregivers compared to care as usual. Both caregiver and patient will be asked to complete online questionnaires at baseline (T0), three months after baseline (T1), six months after baseline (T2) and nine months after baseline (T3), but only the caregivers will receive the support program. In figure 1, the flowchart of the study is presented. In a subgroup of caregivers, we will explore experiences with the support program through interviews.

Study population

Caregiver-patient dyads will be recruited through a nationwide ALS/PMA database and via the website of the Dutch ALS Center. The study will also be announced on websites of ALS/PMA patient associations. Patient and inclusion criteria are 1) the caregiver is the partner of the ALS or PMA patient; 2) the caregiver is 18 years or older; 3) caregiver and patient are proficient in Dutch to fill out the questionnaires; 4) caregiver and patient have internet access. When patients are not able or not willing to complete online questionnaires, caregivers are still eligible to join the support program provided the patient consents. The inclusion criteria remain in force.

Sample size

The sample size calculation was based on Hospital Anxiety Depression Scale (HADS) data of informal caregivers in a previously completed study.[6] The total number of caregiver-patient dyads needed to detect a clinically relevant difference[32] of 3.65 points, with a Standard Deviation of 7.3 between the groups at T2, with an alpha of 0.05 and a power of 80%, is 116 caregiver-patient dyads (58 dyads in each group). Taking into account an attrition rate of 20%, we aim to include 140 caregiver-patient dyads in total.

Procedure

Caregiver-patient dyads recruited via the national ALS/PMA database will be contacted by telephone. In this telephone call, the dyad will receive information about the study. When dyads are interested in participating, the inclusion criteria will be checked. Eligible dyads receive the study information letter per mail. One week after sending the information letter, caregivers will be contacted by telephone. Caregivers who do not want to participate will be asked for their reasons for not participating and we will assess their burden of caregiving with the one item, Self-Rated Burden scale (SRB).[33]

Caregiver-patient dyads can find information about the research and can apply to participate on the Dutch ALS Center website. Thereafter, the researcher will send the research information letter. One week after sending the information letter, caregivers will be contacted by telephone to answer questions and to check the inclusion criteria.

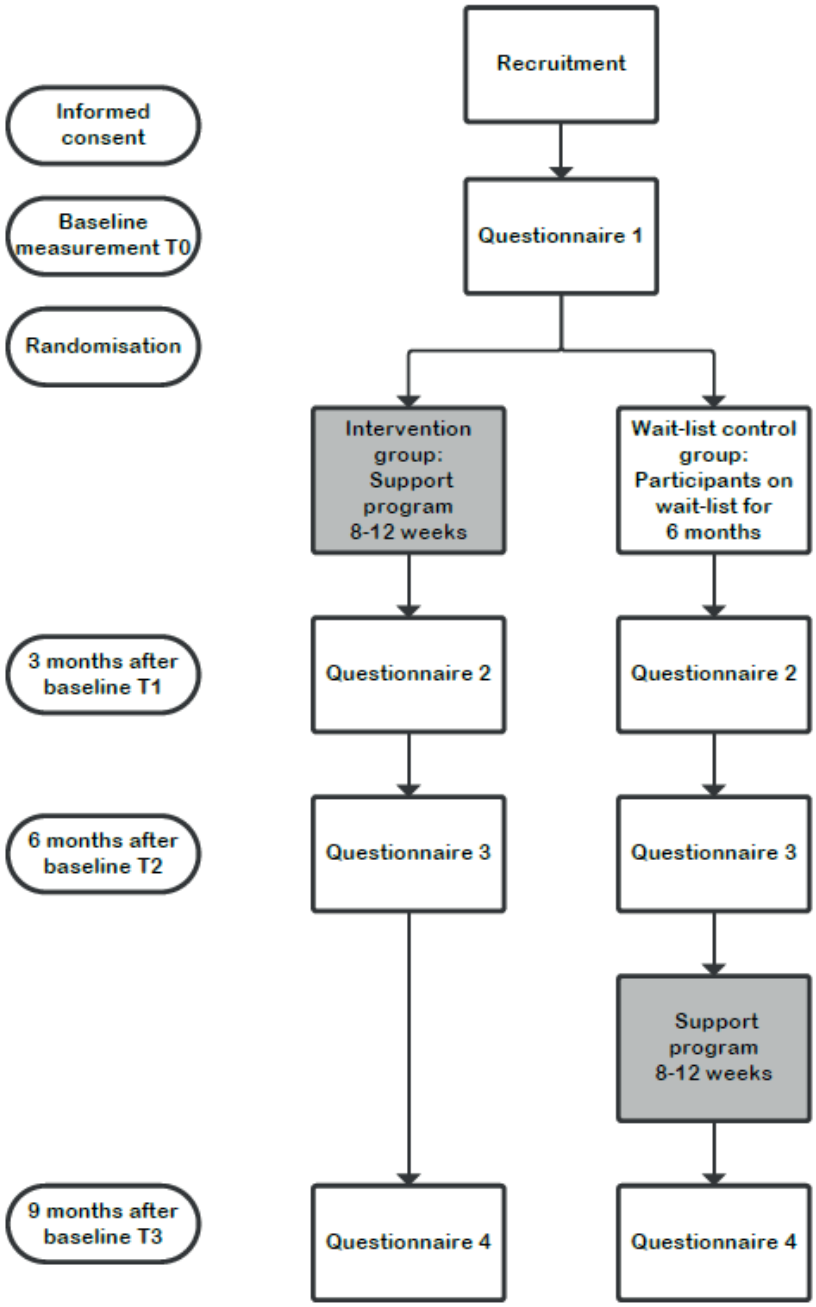

Figure 1. Flowchart study

Dyads are asked to return the signed informed consents by postal mail. Once the informed consents have been received, participants are sent an invitation via e-mail to fill out the first assessment (T0).

Randomization

After completing the first assessment, dyads will be randomized into the wait-list control or experimental condition by the researchers according to a computerized programmed randomization scheme. Randomization will be stratified for the degree of functional impairment of the patient (Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised, using the cut off score for severe-very severe disabilities ≥24)[34, 35], presence of behavioral problems of the patient (Amyotrophic Lateral Sclerosis-Frontotemporal Dementia-Questionnaire, using the cut off score for mild behavioral changes ≥22)[36] and gender of the caregiver.

The intervention

The content of the support program for informal caregivers is based on an online intervention aimed at partners of patients with cancer.[37, 38] This intervention, based on ACT, was adapted to the specific needs of ALS caregivers. We interviewed 21 ALS caregivers about their support needs[17] and added information and exercises related to these needs to the support program. Next, we asked 6 ALS caregivers and professionals in ALS/PMA care and research (physicians, psychologists and researchers) to provide feedback on the content of the program. Based on their feedback, text materials were adjusted and the web-based application was developed. In a usability test, five partners were observed while using the web-based application and they were asked to evaluate it. Their feedback was used to improve the usability of the web-based application.

The support program consists of an introductory face-to-face appointment with a psychologist, 6 psychologist-guided online modules and one closing telephone contact with the psychologist. The total program can be completed in 8 weeks. If caregivers need more time due to personal circumstances, they have the opportunity to work through the total program in 12 weeks. The content of the support program, the topics and the goals of each part are presented in Table 1.

Face-to-face session

Participants will have a one-hour session with a psychologist before they start with the online modules at the residence of the caregiver. The session is protocolized: the psychologist briefly explains the purpose of the intervention, receives information about the caregiving situation, logs in and demonstrates the online program and establishes a working relationship with the participant. Following this session, the caregiver starts with the online modules.

Table 1. Content intervention

Part of intervention	Topics	Goals	Key components
Face-to-face session	• The care situation • Wellbeing caregiver • Information about support program • Log in online modules	To receive information about the care situation and establishing a relationship between the psychologist and the caregiver. To inform about caregiver burden and start online modules.	• Psychoeducation
Online module 1 Coping with your emotions and thoughts	• Dealing with and expressing emotions • Recognizing thoughts	To recognize emotions and encourage caregivers to allow, express and share emotions that can arise. To recognize dysfunctional thoughts and rumination. Change the way the caregiver relates to thoughts/ to create distance from thoughts.	• Acceptance • Cognitive defusion • Mindfulness
Online module 2 The art of communication	• Communication style • Communicating about sensitive topics • Communication about providing care	To improve the overall communication and to communicate with the patient about sensitive topics and providing care in the future.	• Communicating about what really matters • Mindfulness
Online module 3 Your resilience plan	• Dealing with continuous stress • Moments of relaxation • Using your sources	To make a resilience plan that may allow caregivers to maintain healthy during this stressful period by taking care of themselves.	• Acceptance • Mindfulness
Online module 4 What is really important	• Values in relationship • Values in life	To identify the values of the caregiver in different areas of life and to plan action to meet these values.	• Values • Commited action
Online module 5 Moments of joy	• Positivity during difficult times • Celebrate the relationship	To seek, enjoy and cherish the positive moments in the relationship and in life.	• Mindfulness • Committed action • Mindfulness
Online module 6 A good last period	• Life story of the patient • Communication in this last phase • Beautiful memories • Being grateful	To create a beautiful last period with the loved ones and to make memories with the patient for the future.	• Acceptance • Communicating about what really matters • Committed action • Mindfulness
Telephone call	• Any questions • Finish the support program	To offer support with regard to any issues and close the support program.	

Online modules

The online part consists of 6 online modules, each module is directed at a specific theme. All modules start with an introduction directed at the theme of the module, followed by psychological exercises. The content of the online modules is focused on the following key components: 1] acceptance (embracing the private events without unnecessary attempts to change them[39], 2] values (identifying valued domains of life[40]), 3] committed action (actions to pursue one's values 40), 4] mindfulness (training conscious awareness and attention from one moment to the next moment 41), 5] communication about what really matters, 6] cognitive defusion (change the way one interacts with or relates to thoughts by altering the contexts in which they occur 39). Participants also receive practical information, tips and references to relevant websites, organizations and other sources of information and support associated with the theme of the module. They are able to get in contact with other participating caregivers of patients with ALS or PMA, using the online program. They have an online personal profile and can send each other private messages. Participants can also share tips and advice with fellow participants.

The same psychologist who visited the participant for the face-to face session provides online feedback including feedback on the completed exercises, a reflection on the progress of the participant and a reaction to any questions or difficulties.

Telephone contact

The program ends with a telephone call with the psychologist. During this call, the caregiver can ask for advice for specific problems and discuss questions that came up after completing the last module.

Guidance

The support will be provided by psychologists who are trained to provide the intervention.

Assessments

All quantitative assessments are self-report measures and will be administered online. Overviews of the questionnaires for caregivers and patients and their time of assessment are provided in Table 2 and 3. Participants who discontinue the intervention will be asked to complete study follow-up assessments. Semi-structured qualitative interviews will be conducted by telephone.

Primary outcomes measure

Caregivers' psychological distress. Psychological distress will be measured using the Hospital Anxiety and Depression Scale (HADS).[42, 43] This scale consists of 14 items reflecting symptoms of anxiety and depression by 7 items each. Items are scored on a 4-point scale and total scores range from 0 to 42. Furthermore, a total score for the subscales depression and anxiety can be calculated. The internal consistency for the total scale and both subscales is sufficient to high (Cronbach's alpha

Table 2. Measurement overview caregivers

Outcome	Instrument	Measurement[1]			
		T0	T1	T2	T3
Socio-demographics					
Caregiver, patient, and care characteristics	iMTA Valuation of Informal Care Questionnaire	x			
Primary outcome					
Psychological distress	Hospital Anxiety and Depression Scale	x	x	x	x
Secondary outcomes					
Quality of life	Care-related Quality of Life -7+ Care-related Quality of Life - VAS	x	x	x	x
Burden	Zarit Burden Interview + Self-Rated burden Scale	x	x	x	x
Mediator					
Self-efficacy	Revised scale for caregiving self-efficacy	x	x	x	x
Covariates					
Satisfaction with relationship	Satisfaction Questionnaire	x	x	x	x
Social Support	Multidimensional Scale of Perceived Social Support	x	x	x	x
Behavioral changes patient	Amyotrophic Lateral Sclerosis-Frontotemporal Dementia- Questionnaire	x	x	x	x
Physical functioning patient	Amyotrophic Lateral Sclerosis Functional Rating Scale- Revised	x	x	x	x
Evaluation					
Evaluation intervention	Client Satisfaction Questionnaire + Self developed scale		x*		x**

[1] T0= Baseline, T1= 3 months, T2= 6 months, T3= 9 months
* only for the intervention group
** only for the wait-list control group

Table 3. Measurement overview patients

Outcome	Instrument	Measurement[1]			
		T0	T1	T2	T3
Secondary outcomes					
Quality of life	McGill Single Item Scale	x	x	x	x
Psychological distress	Hospital Anxiety and Depression Scale	x	x	x	x
Covariates					
Self-perceived as burden	Self-perceived Burden Scale- 1 item	x	x	x	x

[1] T0= Baseline, T1= 3 months, T2= 6 months, T3= 9 months

ranging from .71 to .90). The test-retest reliability for the total scale and both subscales proved to be high (correlation coefficient ranging from .86 to .91).[42, 44]

Secondary outcomes measures

Caregiver burden. The Zarit Burden Interview (ZBI) will be used to measure caregiver burden by evaluating disease impact on caregivers' quality of life, psychological suffering and impact on social and family relationships.[45] We will use a short version of 12 items, which has shown to have comparable psychometric properties to the full version that consists of 22 items.[46] The ZBI contains a 0–4 point scoring system with the following answering options: never, rarely, sometimes, quite frequently and nearly always. The questionnaire yields a maximum score of 48. A score ≥17 indicates a high burden. The ZBI short form shows good validity, internal consistency, and discriminative ability.[47]

Burden of caregiving will additionally be measured with the Self-Rated Burden scale (SRB).[33] The SRB is a single question in which informal caregivers are asked how burdensome they feel caring for or accompanying the patient at that moment. The scores range between '0' (no burden) and '100' (the care is much too hard). The SRB is a valid and reliable question and it can be used for a quick screening of caregivers at risk.[33]

Caregiver quality of life. Caregivers' quality of life will be assessed using the Care Related- Quality of Life (CarerQoL).[48] The CarerQoL combines a description of the burden of caregiving on seven care dimensions (CarerQoL-7) with a valuation component (CarerQoL-VAS) assessing general quality of life in terms of happiness. The CarerQoL-7 is provides answering categories 'none' (1), 'some' (2), and 'many' (3). The CarerQoL-VAS contains 0, 'completely unhappy' and 10 'completely happy' as endpoints. The psychometric properties of the CarerQol were shown to be satisfactory.[48-50]

Patients' quality of life. Patients' self-rated quality of life will be measured using the McGill Quality of Life Questionnaire (MQOL)[51], which is designed to measure the quality of life of patients with a terminal illness. In order to burden the patients as little as possible, we will only use the single item scale (SIS) which assesses the overall quality of life with answer scores ranging from 0=very bad till 10=excellent.

Patients' psychological distress. Patient's psychological distress will be measured with the HADS.

Mediator

Caregivers' self-efficacy. Caregivers' beliefs about their capacity to carry out caregiving tasks will be measured using the Revised Scale for Caregiving Self-Efficacy.[52] The original version of the instrument consisted of 15 items within 3 subscales; self-efficacy for obtaining respite, responding to disruptive patient behaviors, and controlling upsetting thoughts about caregiving. The disruptive patient behaviors scale is not suitable for our target population and is omitted.

Caregivers are asked to indicate on a scale of 0 (absolutely cannot do) -100 (certainly can do) how confident they are with respect to items such as "how confident are you that you can control worrying about future problems that might come up with [patient]". All subscales demonstrate strong internal consistency and adequate test-retest reliability.[52] We added 3 additional questions based on the Job Content Questionnaire aimed at the control that caregivers perceive over fulfilling the caregiver tasks.[53]

Covariates

Caregivers' social support. Caregivers' experience of social support will be measured using the Multidimensional Scale of Perceived Social Support (MPSS)[54]. The MPSS consists of 12 items and is aimed at different sources of social support (family, friends, and significant other). The items are scored on a 7-point Likert scale ranging from 1 (very strongly disagree) to 7 (very strongly agree). The total score is calculated by adding up the scores of all items, resulting in a range of 12-84. A higher score indicates stronger social support, with scores ≥79 corresponding to an experience of strong support. MPSS has proven to be a psychometrically valid instrument, with good test-retest reliability and adequate validity among varying populations[54-56]

Caregivers' satisfaction with relationship. Caregivers' satisfaction with the relationship with the patient will be assessed using Satisfaction Scale.[57] The questionnaire consists of 4 satisfaction items which are rated on a scale ranging from 1 (*not satisfied*) to 5 (*satisfied*). A total score is calculated by adding up the scores of the 4 items, with a higher score indicating more satisfaction with the relationship. The items refer to caregivers' experience during the last month. The satisfaction scale shows reasonable internal consistency.[58]

Patients' behavioral changes. Behavioral changes in ALS patients will be assessed with the Amyotrophic Lateral Sclerosis-Frontotemporal Dementia-Questionnaire (ALS-FTD-Q).[36] The questionnaire asks the caregiver to compare the patient's current behavior with his/her behavior 3 years ago. It consists of 25 items with a total score range of 0-100 (≥22 indicating mild behavioral changes and ≥29 corresponding with significant behavioral changes). The ALS-FTD-Q shows good internal consistency (Cronbach's $\alpha = 0.92$) as well as construct validity.[36]

Patients' physical functioning. The physical functioning of ALS patients will be assessed using the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALS-FRS-R).[35] The scale consists of 12 items with 0-4 point scores in order to measure limb, bulbar, and respiratory dysfunction. An example is the item 'Walking' with answer scores 0=normal to 4=is unable to consciously move legs. Overall scores range from 0-48, with higher scores indicating better physical functioning. The ALS-FRS-R demonstrates strong internal consistency as well as construct validity.[35] This questionnaire will be completed by the caregiver.

Patients' perception of being a burden. Patient's own feelings of being a burden for the caregiver will be measured using one item of the Self Perceived Burden Scale (SPBS): "I feel that I am a burden to my caregiver".[59] This statement is rated on a scale of how often patients feel this way, from 'none of the time' (1) to 'all of the time' (5). Higher scores indicate that the patients perceived themselves to cause a higher burden to their caregivers.

Evaluation of the intervention

Satisfaction with received support. To measure the satisfaction of the caregiver for the support they received, the 8-item Client Satisfaction Questionnaire (CSQ-8) is used.[60] All items are scored on a 4-point scale ranging from 1 to 4. Response options differ from item to item. An example is "How satisfied are you with the amount of help you have received?" (for which the response options range from 1='Quite dissatisfied to 4='Very satisfied'). An overall score is calculated by summing and ranges from 8 to 32, with higher scores indicating higher satisfaction. The Dutch translated version of the questionnaire shows high internal consistency (.91).[61]

Evaluation support program. Additionally, a scale to evaluate the intervention was developed. The participant is asked to rate the intervention in general and the different components of the intervention such as the psychological exercises, contact with the psychologist who provided the feedback and contact with other informal caregivers. Participants are asked to rate every component on a 0-10 scale, the questionnaire consists of 9 questions.

Experiences with support program. Semi-structured interviews to explore the experiences of the caregivers with the support program will be carried out after subjects complete the support program. Participants will be selected via purposive sampling on demographic variables (age, sex, disease stage patient). Interviews will be held by a researcher, using a topic list with the following topics: experiences with support program, user-friendliness, use of the support program, valuable, missing and redundant elements of the support program and recommendations for change. The interviews will last approximately 1 hour and will be recorded. Participants will be included until data saturation is reached.

Demographics and description of the care situation

Demographics and care situation. The iMTA Valuation of Informal Care Questionnaire (iVICQ) is a questionnaire which facilitates an accurate description of providing informal care, its effects on informal caregivers.[62] We used the sections of the background information of patients and caregivers, the informal care situation and questions to economically validate informal care as a directory for our questions regarding these subjects.

Questions to assess the working mechanism of the support program

The support program aims to improve feelings of control over caregiving and reduce psychological distress. Therefore, at the end of every online module the caregiver is asked two questions about 'feelings of control over executing caregiving tasks' and 'the level of distress they experience', at that moment on a VAS scale.[63]

Monitoring adherence to the intervention modules

In order to assess the use and the adherence of the online modules we will collect log data of the participants such as the frequency of logging in, the duration of logging in, which parts of the modules are downloaded and which functions are used.

Data management

All personal data will be coded, removed from the data for analysis and stored separately. Only designated research staff will have access to the keys linking the data with the personal information. The research team will have access to the final dataset. Data management and monitoring of the trial will be performed by qualified personnel according to standard operation procedures of the Brain Center Rudolf Magnus, University Medical Center Utrecht.

Analyses

Statistical analyses

Descriptive statistics will be used to report demographic variables, clinical outcomes, and the use of the different modules. Group differences in primary and secondary outcomes will be compared with linear mixed model analysis, in which the mediator and covariates will be included. Statistical analysis will be performed primarily according to intention- to-treat and secondarily according to per-protocol principles. The intention to treat analysis will include data of all included caregivers, regardless of their adherence to the intervention or their missing data.

In the per-protocol analyses we will only include caregivers who completed at least 4 modules (66.7%) and the T2 measurement. All hypotheses will be tested 2-sided, with a critical value of 0.05. Effect sizes on the primary outcome variable (HADS total) will be calculated with Cohen's D using the means and pooled standard deviations of the two groups.

Interview analyses

Interviews will be transcribed and analyzed thematically.[64] The texts will be broken down into fragments based on content and fragments will be labeled with a code using NVIVO 10.[65, 66] Once the coding of all interviews is completed, codes will be sorted according to similarities and overarching themes and subthemes will be identified.

Discussion

To our knowledge, this will be the first study to evaluate a blended support program for caregivers of ALS and PMA patients. The program is aimed at enhancing feelings of control over caregiving tasks using ACT principles. Previous research on ALS caregiving revealed increasing levels of psychological distress in caregivers, a lack of existing interventions and an urgent need for support.[7, 21] ACT interventions have proven to reduce psychological distress in other caregiver populations[27, 28] and are valuable in contexts with circumstances that are unchangeable.[23, 24]

A strength of this intervention is the blended approach: face-to-face support in combination with online support. Due to the many hours ALS and PMA caregivers spend on providing care, they often experience a lack of personal time[17], which reduces the opportunity to access traditional forms of support. Therefore, the blended approach may provide support in a more time-efficient manner, as caregivers can access information and exercises any time at home via an online platform.

Although previous research has provided information on factors associated with psychological distress and burden e.g.[15], the underlying process is still unclear due to a gap in research on personal factors related to the caregiver. The use of a theoretical framework is considered as another strength since it helps to gain insight in whether the demand-control theory is applicable to the caregiver situation in ALS[18] and will provide knowledge on the influence of factors such as control and mastery in relation to psychological distress and burden. This will provide information to understand how, when and for whom the intervention will be effective.

Further, caregivers, psychologists and social workers were involved in both the development process of the intervention and the design of the study. Due to their involvement, we were able to develop an intervention that meets the needs and wishes of caregivers and includes the most important themes according to professionals. Caregivers and professionals will also be involved in the next steps of the research such as the recruitment and the dissemination of the results of the study. Previous studies indicated that engaging the target group increases study enrollment and may enhance the uptake and the acceptance of interventions.[67, 68]

Another strength of the study design is the mixed method approach; questionnaires and interviews will be used to evaluate the program which enables a throughout evaluation and may lead to further improvement of the support program.

The support program may also have some weaknesses. First of all, the online part of the support program might be an obstacle for some caregivers due to a lack of information and communication technology literacy. These caregivers might prefer to receive traditional face-to-face support.

Another limitation might be that the intervention is only focused on partners, which means that primary caregivers who have another type of relationship with the patient are excluded while they might be in need of support. When the intervention has proven to be effective, it might be worthwhile to develop an adapted version for primary caregivers with other relationships to the patient.

A limitation of the study design might also be contamination with care as usual. In the last couple of years, the value and the importance of the social environment of patients has been emphasized. This has led to a stronger focus on caregivers in standard care; care facilities are encouraged to involve caregivers in their care plans. Due to this recent shift, the support for caregivers might be improved and it may be more difficult to demonstrate a significant difference when we compare care as usual with our support program. However, when caregivers perceive the support program as more user-friendly than care as usual this encourages the use of support program in standard care.

To conclude, this study will provide insight into the effects of a blended support program for informal caregivers of patients with ALS and PMA by targeting feelings of control over caregiving tasks using ACT principles. The program could potentially benefit caregivers, and might affect patients' wellbeing indirectly.

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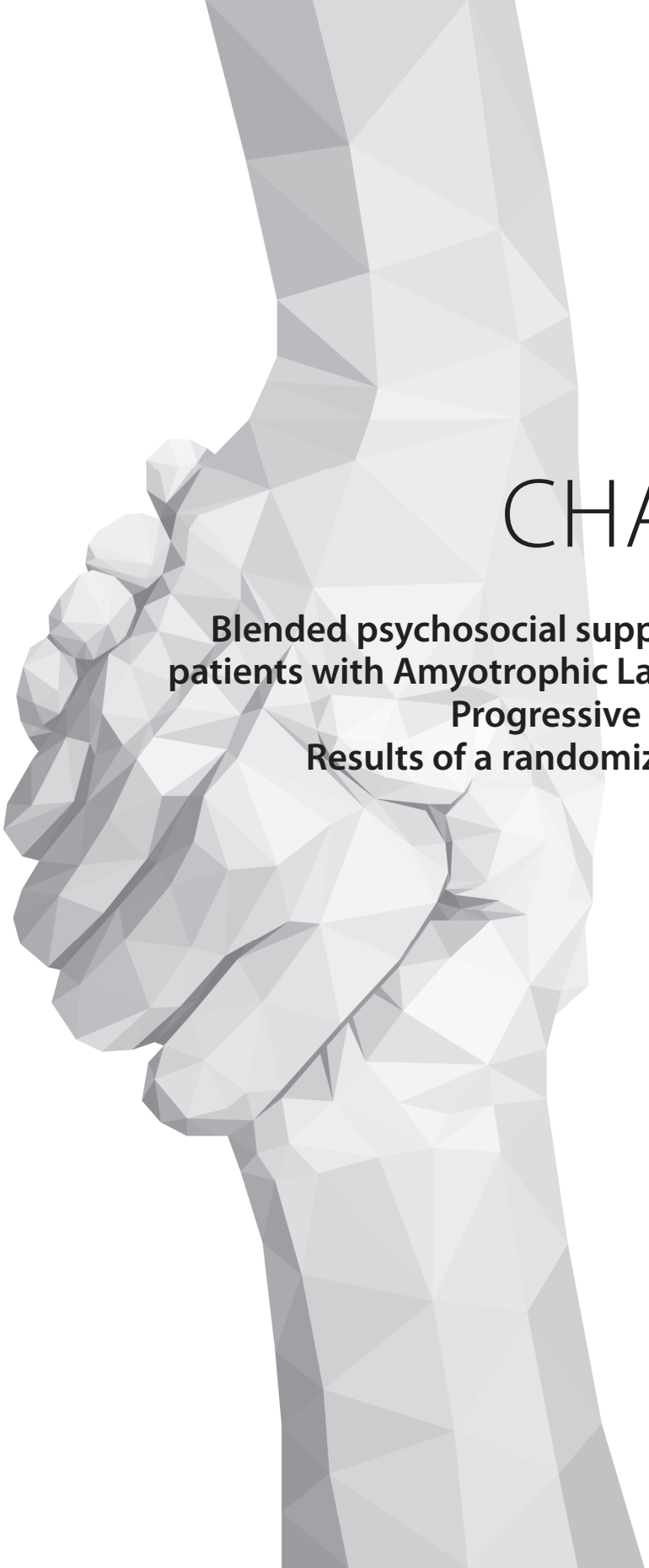

CHAPTER 7

Blended psychosocial support for partners of patients with Amyotrophic Lateral Sclerosis and Progressive Muscular Atrophy: Results of a randomized controlled trial

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Under review

Abstract

Objective: To evaluate whether a blended psychological support program for caregivers of patients with Amyotrophic Lateral Sclerosis (ALS) and Progressive Muscular Atrophy (PMA), aimed at enhancing feeling of control over caregiving, reduces psychological distress.

Methods: A randomized controlled trial using a wait-list control design was conducted. Caregiver-patient dyads were randomly assigned to either the support program (n=74) or to a wait-list control group (n=74). The support program, based on Acceptance and Commitment Therapy, consists of 1 face-to-face contact, 6 online guided modules and 1 telephone contact. Participants filled in questionnaires at baseline, 3 and 6 months. Caregivers' feeling of control over caregiving was assessed using two self-efficacy measures. Primary outcome was caregivers' psychological distress. Secondary outcomes included caregiver burden, caregiver quality of life and patients' quality of life and psychological distress. Intention-to-treat and per-protocol analyses were performed to assess the effects of the intervention using linear mixed models.

Results: The support program had no effect on the primary or secondary outcomes, despite a significant positive effect on the intervening variable self-efficacy with regard to control over thoughts. Caregivers evaluated the support program positively but almost half of the caregivers did not complete the intervention.

Conclusions: The support program did not reduce distress of partners of patients with ALS but may be beneficial by increasing feeling of control over the caregiving situation.

Introduction

Informal caregivers play a crucial role in the care for patients with Amyotrophic Lateral Sclerosis (ALS) and Progressive Muscular Atrophy. ALS and PMA are progressive and fatal diseases in which the physical functioning of patients deteriorates and cognitive and behavioral changes can arise, resulting in increasing care needs over time.[1] For both patients and their caregivers this might result in feelings of helplessness[2], subsequently making it difficult to experience a feeling of control over their situation.[3] Experiencing high care demands and insufficient control over the caregiving situation increases the risk of psychological distress in caregivers.[4] In caregivers of patients with ALS distress increases over time but psychosocial evidence-based interventions are lacking.[5]

Although caregivers express a need for individual psychosocial support[6], they frequently withdraw from seeking or accepting support.[7] They report difficulty in balancing their personal time with caregiving responsibilities.[8] Blended care combines face-to-face healthcare with online healthcare and could bridge the gap between the need for support and lack of time.[9] Acceptance and Commitment Therapy (ACT) has proven to be effective in reducing psychological distress in caregivers of other patient populations.[10, 11]

This study evaluates the effectiveness of a blended psychosocial support program, based on ACT, aimed at enhancing feelings of control over caregiving, in order to reduce psychological distress in caregivers of patients with ALS and PMA. The indirect effect of the support program on patients' wellbeing and participants' adherence and satisfaction with the program were also studied.

Methods

Study design and procedures

The study protocol has been described in detail.[12] In this randomized controlled trial (RCT), caregiver-patient dyads were randomly allocated to the support program or to a 6-months wait-list control group, in addition to usual care. Care as usual is provided by multidisciplinary ALS care teams and is mainly focused on patients, but partners who experience problems are able to receive support from a social worker or psychologist.

Both caregivers and patients filled in online questionnaires at baseline (T0), after the intervention (3 months after baseline, T1) and 3 months after finishing the intervention (T2). Patients could provide consent for the caregiver to participate, with or without own study participation. Patients' consent was needed since caregivers filled in questionnaires about patients' functioning. After caregivers and patients provided informed consent and caregivers completed the baseline measurement, dyads were randomized.

Randomization in a 1:1 ratio was stratified by gender, functional impairment and behavioral problems of the patient and was conducted by the researcher (JW) using a computer-generated randomization sequence, allowing concealment for the next allocation. Due to the nature of the intervention, blinding of participants was not possible.

The study was approved by the Medical Ethics Committee of the University Medical Center Utrecht (16-273-D) The trial was registered at the Netherlands National Trial Register (NTR5743). All participants provided informed consent. The study is reported in accordance with the CONSORT guidelines.[13]

Participants

Participants were recruited through a nationwide ALS/PMA database and via the Dutch ALS Center website. Eligible dyads met the following criteria: 1) the caregiver is the partner of the ALS or PMA patient; 2) the caregiver is 18 years or older; 3) caregiver and patient are proficient in Dutch; 4) caregiver and patient have internet access.

Intervention

The blended psychosocial support program consisted of 1 face-to-face contact, 6 online guided modules and 1 closing telephone contact and was guided by a psychologist. The program was solely offered to the caregiver and could be worked through in 8-12 weeks. Modules were offered in a fixed sequence in which participants received access to the next module after 1 or 2 weeks. The content of the support program was focused on Acceptance and Commitment Therapy and based on an online intervention aimed at partners of patients with cancer .[14, 15] We adapted this program to the specific needs of caregivers of patients with ALS and PMA. Participants started the program with a face-to-face session with a psychologist who briefly explained and demonstrated the program and retrieved information about the situation. After this contact, the caregiver started with the first online module. Every module was focused on a specific theme (e.g. coping with emotions and thoughts, communication) and contained psychoeducation, psychological exercises, mindfulness exercises and practical information and references to relevant websites. After completing each module, participants received feedback on the exercises from the psychologist. Participants could get in contact with other participants through private messaging and they could share advices using a forum. The support program was closed with a telephone call, in which the caregiver could ask for advice. Participants were guided through the program by two psychologists who were trained to provide the support program and personalized feedback, and who could be contacted at any moment during the program.

Outcomes

Primary outcome

The primary outcome of this study was psychological distress of the caregiver, assessed with the Hospital Anxiety and Depression Scale (HADS; range 0-42).[16]

Secondary outcomes

The secondary outcome measures of this study included:

1. Caregiver burden, assessed with the Zarit Burden Interview (ZBI; range 0-48)[17]
2. Caregivers' quality of life, measured with the Care Related- Quality of Life (CarerQoL; range 7-21 + CarerQol Vas; range 0-10).[18]
3. Patients' quality of life, measured using the single item scale of the McGill Quality of Life Questionnaire (MQOL; range 0-10).[19]
4. Patients' distress, assessed with the HADS.[16]

Intervening variable

The intervening variable in this study was feeling of control over caregiving which was measured as caregivers' self-efficacy over caregiving:

1. Caregivers' beliefs about their capacity to obtain respite from caregiving was measured using the Respite care subscale of the Revised Scale for Caregiving Self-Efficacy (RSCSE-Resp) (per subscale, range 0-100).[20]
2. Caregivers' beliefs about their ability to control distressing thoughts about caregiving was measured using the 'Controlling upsetting thoughts about caregiving' subscale of the RSCSE (RSCSE- Contr).
3. Perceived control over fulfilling caregiver tasks was measured with three questions adapted from the Job Content Questionnaire (range 0-9).[21]

Covariates

The analyses of the caregiver outcomes were adjusted for the baseline scores of:

1. Caregivers' social support, measured with Multidimensional Scale of Perceived Social Support (MPSS; range 12-84).[22]
2. Caregivers' satisfaction with the relationship with the patient, assessed using Satisfaction Scale (range 4-20).[23]
3. Patients' physical functioning, assessed using the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALS-FRS-R; range 0-48).[24]
4. Patients' behavioral changes, assessed with the Amyotrophic Lateral Sclerosis-Fronto Temporal Dementia-Questionnaire (ALS-FTD-Q; range 0-100).[25]

The ALSFRS-R and ALS-FTD-Q were completed by caregivers.
The analyses on the patient outcomes were adjusted for the baseline score of the ALSFRS-R and for the baseline score of:

5. Patient's own feelings of being a burden for the caregiver, measured using one item of the Self-Perceived Burden Scale (SPBS; range 1-5).[26]

Satisfaction with support
Satisfaction with the support program was assessed with the Client Satisfaction Questionnaire (CSQ-8; range 8-32).[27] Additionally, the participant was asked to rate the intervention in general and the different components of the intervention on a scale from 0-10. This scale also included a question about suggestions for further development and contained 9 questions in total.

Adherence
Adherence to the intervention and time spent in the program were measured by log files. Participants who completed four modules were considered completers.

Demographics
Demographics and information about the care situation were administered using the The iMTA Valuation of Informal Care Questionnaire (iVICQ).[28]

Statistical analyses
Sample size calculation
A sample size of 58 per group was needed to detect a clinically relevant difference of 3.65 points (SD=7.3) on the HADS[16] between the groups at T2, with an alpha of 0.05 and a power of 80%. Anticipating a drop-out of 20% between baseline and T2, we aimed to include a total of 140 caregiver-patient dyads.

Effectiveness analyses
First, data were analysed on an intention-to-treat principle; all caregivers with follow-up data were included whether or not they completed the intervention or the follow-up assessments . Linear mixed models (LMM) were used to investigate differences in the course of the outcome measures between the two groups. All analyses were performed using fixed effects for group, time and their interaction, as well as a random intercept per subject and a random slope for time. All caregiver models included relevant covariates: caregivers' social support, caregivers' satisfaction with their relationship, patients' physical functioning and patients' behavioral changes. Patient models were corrected for the baseline scores of patients' self-perceived burden and patients' physical functioning.

Additionally, per-protocol analyses were performed including only caregivers who attended four (66.7%) or more online modules. Missing data were accounted for by the statistical techniques used (LMM).[29] Analyses were performed with SPSS version 25.

Results

Participants

The recruitment took place from July 2017 to March 2018 and the trial was completed in February 2019. A total of 538 dyads with ALS/ PMA were assessed for eligibility and 148 caregivers and 101 patients with ALS/PMA were included in the study (Figure 1 and 2). After randomization, 74 caregivers started with the support program and 74 caregivers were on a wait-list for the support program. Characteristics of the caregivers and the patients for whom they provide care are shown in Table 1. The majority of caregivers was female (64.9%); their mean age was 61 years. There were no significant differences in demographic and clinical outcome measures between patients who participated in the study (*n*=101) and patients who only provided consent for their partner to participate (*n*=47).

A total of 28 (19%) caregivers dropped out of the study (i.e. they indicated they would no longer participate in any part of the study, filling in questionnaires or the support program). The most common reason for drop-out was the death of the patient (*n*=16). Drop-outs had partners with a significantly lower physical functioning score (ALSFRS-R; *M*=26. 9, *SD*=9.0) compared to study completers (*M*=32.4, *SD*=9.4, *p*<.01). There were no further significant differences between drop-outs and study completers.

Support program adherence

Caregivers could stop with the support program, but still participate in the study by filling in questionnaires. The support program was completed by 38 caregivers (51%); 28 caregivers stopped with the intervention prematurely, and 8 dropped out of the study before completing the intervention. The main reasons reported for not completing the intervention were: a lack of time for receiving support (*n*=9), no perceived value of the program (*n*=4), the program was too confronting (*n*=2) and illness of the caregiver (*n*=2) (Figure 1). Completers and non-completers did not differ significantly as far as baseline caregiver and patient characteristics were concerned. Caregivers completed the program in an average of 8 weeks and spent a mean of 1 hour and 26 minutes per module (range 7 minutes - 4 hours and 18 minutes).

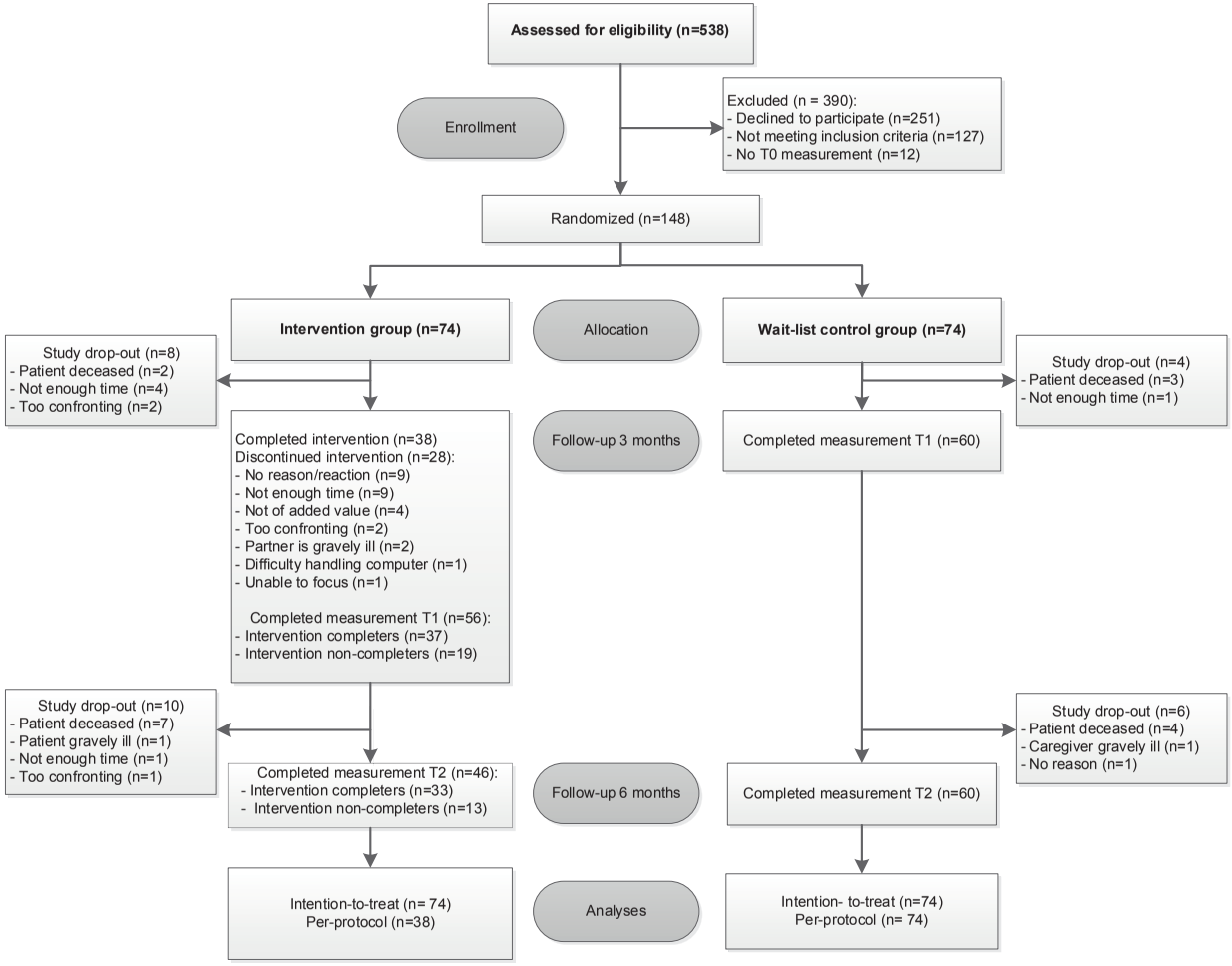

Figure 1. Flowchart caregivers in study

Table 1. Characteristics of the caregivers in the trial and the patients for whom they provide care (*n*=148)

	Intervention (*n*=74)	**Wait-list (*n*=74)**
Caregiver characteristics		
Gender, *n* (% female)	48 (64.9)	48 (64.9)
Age in years, mean (SD)	61.8 (10.6)	61.3 (9.8)
Education level, *n* (%)		
Low	28 (37.8)	35 (47.3)
Medium	16 (21.6)	19 (25.7)
High	30 (40.5)	20 (27.0)
Occupation, *n* (%)		
Not working	45 (60.8)	45 (60.8)
Paid work/employment	29 (39.2)	29 (39.2)
Country of birth, *n* (%)		
The Netherlands	68 (91.9)	67 (90.5)
Other	3 (4.1)	2 (2.7)
Missing	3 (4.1)	5 (6.8)
Providing care tasks, *n* (%)		
Yes	59 (79.7)	59 (79.7)
Hours providing care per week, median (inter quartile range)	35 (22-60)	38 (21-56)
Receiving support to deal with caregiving situation, *n* (%)		
Yes	19 (25.7)	37 (50.0)
Patient characteristics		
Gender, *n* (% female)	26 (35.1)	27 (36.5)
Age in years, mean (SD)	62.3 (11.0)	62.9 (8.9)
Diagnosis, *n* (%)		
ALS	52 (70.3)	54 (73.0)
PMA	22 (29.7)	20 (27.0)
Time since diagnosis in months, median (inter quartile range)	22.5 (8.0-34.3)	16.00 (9.8-44.3)
Level of functioning, mean (SD)		
ALSFRS-R	31.7 (9.8)	31.0 (9.5)
ALS-FTD-Q	16.3 (11.8)	17.2 (13.9)
Country of birth, n (%)		
The Netherlands	72 (97.3)	65 (87.8)
Other	0 (0.0)	2 (2.7)
Missing	2 (2.7)	7 (9.5)

ALS: Amyotrophic Lateral Sclerosis; PMA: Progressive Muscular Atrophy; ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; ALS-FTD-Q: Amyotrophic Lateral Sclerosis-Frontotemporal Dementia-Questionnaire; Educational level: low = did not complete secondary school-completed low level secondary school; medium = completed medium level secondary school; high = completed upper level secondary school and/or university degree

Effectiveness support program analyses

There were no significant effects on psychological distress, despite a significant difference between the intervention group and wait-list control group in caregivers' self-efficacy with regard to controlling thoughts about caregiving (RSCSE- Contr; Table 2). Nor were there any significant differences in the other caregivers' outcomes and intervening measures (burden, quality of life and the other self-efficacy scales) between the intervention group and the wait-list control group. Furthermore, no significant differences in psychological distress or quality of life of patients were found between the intervention group and the wait-list control group. The per-protocol analyses confirmed the results of the intention-to-treat analysis (Table 3).

Satisfaction with the blended support program

Participants were satisfied with the interventions and scored a mean total of 25.57 (SD 3.8) on the CSQ-8. Participants rated the overall program with a mean score of 7.6 (SD 1.3) and scored the contact with the professional with a mean 8.4 (SD 1.3). With regard to the specific components of the program, caregivers were least satisfied with the peer contact and mindfulness exercises (Table 4).

Discussion

The blended psychological support program was appreciated by caregivers but did not lead to reduced psychological distress, caregiver burden or quality of life in caregivers, nor to reduced quality of life or psychological distress in patients. A significant positive intervention effect was found on the intervening variable caregivers' self-efficacy with regard to being in control over thoughts about caregiving. Almost half of the participants did not complete the intervention which may have contributed to the lack of efficacy.

Although an adherence rate of 51% is not rare in online interventions[30], the percentage is considered to be relatively low. The most frequently reported reason for not completing the intervention was lack of time, a commonly reported drop-out reason in caregiver studies.[31] Some of these caregivers expressed that they were so occupied by caregiving that any more obligations were experienced as burdensome. Caregivers of patients with ALS/PMA spend many hours a day on caregiving and the care needed increases over time[32]; in our study, 80 percent of the partners provided care for the patient and they spent a median of 36.5 hours a week on caregiving tasks. For caregivers whose partner was in an advanced disease stage, investing time in an intervention was not beneficial since the caregiving would be coming to an end before long. Therefore, the timing of intervention seems to be crucial. A support program can equip caregivers with tools to deal with the caregiver situation in the long term, which in turn can prevent high levels of distress[33] and prolong the stage during which caregivers feel able

Table 2. Linear mixed model treatment outcome Intervention- vs Wait-list control group

	Wait-list control group Mean (SD)			Intervention completers Mean (SD)			Intervention * time interaction	
Caregivers [a]	**Baseline (*n*=74)**	**3 months (*n*=60)**	**6 months (*n*=60)**	**Baseline (*n*=74)**	**3 months (*n*=56)**	**6 months (*n*=46)**	**b (se)**	***p*-value**
Primary outcome								
HADS	10.84 (7.19)	11.37 (7.70)	11.48 (7.42)	11.38 (7.12)	10.75 (7.62)	11.00 (7.71)	0.09 (0.38)	0.802
Secondary outcomes								
ZBI	13.53 (8.04)	13.62 (7.79)	14.20 (7.58)	13.50 (8.08)	13.18 (7.29)	13.89 (7.76)	-0.19 (0.71)	0.711
CarerQoL-7	10.14 (2.30)	10.10 (2.28)	9.97 (2.09)	10.11 (2.22)	10.63 (2.23)	10.09 (2.23)	-0.11 (0.17)	0.534
CarerQoL-VAS	6.41 (1.43)	6.50 (1.66)	6.25 (1.74)	6.43 (1.55)	6.63 (1.45)	6.43 (1.54)	-0.04 (0.13)	0.735
Intervening variables								
RSCSE- Resp	73.43 (22.31)	69.10 (20.70)	69.63 (23.57)	67.81 (25.05)	72.07 (23.00)	67.30 (22.34)	-1.41 (1.93)	0.465
RSCSE- Contr	64.54 (25.36)	58.33 (24.32)	59.13 (27.16)	60.78 (25.87)	62.71 (26.01)	68.26 (23.04)	-5.39 (1.99)	0.007
JCQa	6.28 (1.85)	6.63 (2.02)	6.32 (2.06)	6.41 (1.89)	6.96 (1.88)	6.93 (1.97)	-0.21 (0.21)	0.325
Patients[b]	**Baseline (*n*=43)**	**3 months (*n*=33)**	**6 months (*n*=31)**	**Baseline (*n*=45)**	**3 months (*n*=30)**	**6 months (*n*=24)**	**b (se)**	***p*-value**
Secondary outcomes								
HADS	10.42 (5.19)	9.82 (5.69)	11.87 (6.98)	9.42 (6.43)	8.00 (6.72)	9.33 (7.75)	0.20 (0.67)	0.767
MQOL	6.79 (1.41)	6.61 (1.85)	6.52 (2.10)	7.07 (1.34)	6.77 (1.94)	6.63 (1.86)	0.22 (0.21)	0.286

[a] Linear mixed model including group, time, intervention*time and adjusted for baseline values of MPSS, SQ, ALSFRS-R, ALSFTDQ.
[b] Linear mixed model including group, time, intervention*time and adjusted for baseline values of ALSFRS-R, SPBS.
Abbreviations: ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; ALS-FTD-Q: Amyotrophic Lateral Sclerosis-Frontotemporal Dementia-Questionnaire; CarerQoL: Care-related Quality of Life; m: mean; HADS: Hospital Anxiety and Depression Scale; JCQa: Job Content Questionnaire 3 adapted items; MQOL: McGill Quality of Life Questionnaire; MPSS: Multidimensional Scale for Received Support; SD: standard deviation; RSCSE- Resp: Revised scale for caregiving self-efficacy subscale respite care; RSCSE- Contr: Revised scale for caregiving self-efficacy subscale controlling thoughts; SE: standard error; SPBS: Self-Perceived Burden Scale; SQ: Satisfaction Questionnaire; ZBI: Zarit Burden Interview.
A significant group-by-time interaction (p<0.05) means a significant difference between groups in outcome over time.

Table 3. Linear mixed model treatment outcome Intervention completers vs Wait-list control group

	Wait-list control group Mean (SD)			Intervention completers Mean (SD)			Intervention * time interaction	
Caregivers [a]	**Baseline (*n*=74)**	**3 months (*n*=60)**	**6 months (*n*=60)**	**Baseline (*n*=38)**	**3 months (*n*=37)**	**6 months (*n*=33)**	**b (se)**	***p*-value**
Primary outcome								
HADS	10.84 (7.19)	11.37 (7.70)	11.48 (7.42)	9.50 (7.35)	8.22 (6.31)	9.30 (7.06)	0.47 (0.41)	0.256
Secondary outcomes								
ZBI	13.53 (8.04)	13.62 (7.79)	14.20 (7.58)	13.13 (8.79)	11.92 (7.43)	12.79 (7.37)	0.50 (0.57)	0.376
CarerQoL-7	10.14 (2.30)	10.10 (2.28)	9.97 (2.09)	10.34 (2.41)	11.16 (1.85)	10.55 (2.09)	-0.24 (0.20)	0.235
CarerQoL-VAS	6.41 (1.43)	6.50 (1.66)	6.25 (1.74)	6.61 (1.46)	6.97 (1.21)	6.76 (1.25)	-0.16 (0.14)	0.262
Intervening variables								
RSCSE- Resp	73.43 (22.31)	69.10 (20.70)	69.63 (23.57)	71.53 (24.97)	74.00 (19.22)	72.30 (18.32)	-2.65 (2.13)	0.214
RSCSE- Contr	64.54 (25.36)	58.33 (24.32)	59.13 (27.16)	67.53 (23.94)	68.81 (21.02)	71.39 (19.13)	-4.93 (2.23)	0.028
JCQa	6.28 (1.85)	6.63 (2.02)	6.32 (2.06)	7.00 (1.64)	7.19 (1.79)	6.82 (2.14)	0.11 (0.24)	0.661
Patients[b]	**Baseline (*n*=43)**	**3 months (*n*=33)**	**6 months (*n*=31)**	**Baseline (*n*=23)**	**3 months (*n*=19)**	**6 months (*n*=15)**	**b (se)**	***p*-value**
Secondary outcomes								
HADS	10.42 (5.19)	9.82 (5.69)	11.87 (6.98)	9.43 (6.71)	8.58 (6.69)	9.73 (7.95)	0.24 (0.75)	0.747
MQOL	6.79 (1.41)	6.61 (1.85)	6.52 (2.10)	7.17 (1.11)	6.68 (2.03)	6.27 (2.02)	0.43 (0.25)	0.089

[a] Linear mixed model including intervention, time, intervention*time and adjusted for baseline values of MPSS, SQ, ALSFRS-R, ALSFTDQ.
[b] Linear mixed model including intervention, time, intervention*time and adjusted for baseline values of the outcome measure, SPBS , ALSFRS-R.
Abbreviations: ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; ALS-FTD-Q: Amyotrophic Lateral Sclerosis-Frontotemporal Dementia-Questionnaire; CarerQoL: Care-related Quality of Life; m: mean; HADS: Hospital Anxiety and Depression Scale; JCQa: Job Content Questionnaire 3 adapted items; MPSS: Multidimensional Scale for Received Support; MQOL: McGill Quality of Life Questionnaire; SD: standard deviation; RSCSE- Resp: Revised scale for caregiving self-efficacy subscale respite care; RSCSE- Contr: Revised scale for caregiving self-efficacy subscale controlling thoughts; SE: standard error; SPBS: Self-Perceived Burden Scale; SQ: Satisfaction Questionnaire; ZBI: Zarit Burden Interview.
A significant group-by-time interaction ($p<0.05$) means a significant difference between groups in outcome over time

Table 4. Evaluation intervention (*n*=53)

Question	Grade 0-10, M (SD)
Does the support program match your situation?	6.2 (2.4)
How do you rate the support program in general?	7.6 (1.3)
How do you rate the information in the support program?	7.9 (1.4)
How do you rate the exercises in the support program?	7.3 (1.8)
How do you rate the mindfulness exercises?	5.7 (2.9)
How do you rate the contact with the professional who provided feedback?	8.4 (1.3)
How do you rate the user-friendliness of the program?	7.8 (1.6)
How do you rate the peer contact functions?	6.7 (2.3)

to support patients at home.[34] But caregivers need to have enough time and mental space to follow the support program, otherwise the program is perceived as burdensome. This is in line with the dual process model which proposes that adaptive coping is a dynamic process of confronting and avoiding stressors associated with loss.[35] Caregivers who are caught up in caregiving and who follow the support program may feel as though they have no respite from dealing with loss, which may have detrimental health effects.[36] Therefore, proactively informing caregivers about possible supportive interventions at an early stage of the disease and offering this repeatedly, seems to be crucial.[33]

The program resulted in an increase in perceived self-efficacy in caregivers. Three types of self-efficacy were measured in this study (self-efficacy with regard to respite care, controlling thoughts and completing care tasks), but the program only increased the self-efficacy with regard to controlling upsetting thoughts. Research in dementia caregivers showed that psychological interventions can improve self-efficacy with regard to obtaining respite.[37] However, respite care and care tasks may be more complicated in ALS due to the severe care needs of the patient.[8] Perceived self-efficacy aimed at organizing respite care and completing care tasks may be strongly influenced by the environment of the caregiver and, therefore, more difficult to influence compared to dealing with thoughts. The program explicitly focused on dealing with thoughts by providing information and exercises on how to deal with upsetting thoughts using ACT. With 'care as usual', professionals often focus on respite care and dealing with care tasks while dealing with negative thoughts is less common.

Contamination with care as usual might have affected the results in this study. Awareness of the difficulties caregivers face while caring for a person with ALS/PMA and their needs has increased[38]. Caregivers nowadays receive more attention from professionals; this may have reduced the contrast between intervention and control condition. In addition, the proportion of caregivers who received professional support focused on dealing with their caregiving situation

at the start of the trial differed between the intervention- and wait-list control group (25.7% and 50%, respectively), which might have affected our results.

Caregivers expressed their satisfaction with regard to the different components of the intervention but were ambivalent towards peer contact and mindfulness. These results are in line with the results of our qualitative evaluation of the intervention.[39] Since some caregivers strongly valued these components, providing them optional is recommended. Caregivers expressed that the match between their needs and the content of the program could be improved by providing the option to follow each online module at a self-chosen order and time. This might improve the adherence rate and the added value of the intervention.[40] E-health seems to be an acceptable and efficient option for receiving support; support becomes available for caregivers who are not able to leave their home due to care responsibilities and the threshold for receiving support is lowered.[41] Choosing when and where they access support gives caregivers the opportunity to take control over the received support.[42] However, the preferred modus might differ per caregiver; offering customized care in line with the caregiver's preferences is advised.

Limitations

Some partners expressed that their main motivation for participating in this trial was to take part in ALS research rather than a need for support. Patients with ALS/PMA and their family members are often eager to cooperate in research in order to contribute to finding the cause of the disease.[43] These caregivers were possibly less motivated to complete the intervention which might have affected our results. Another limitation might be that the levels of caregivers' distress in our study were relatively low compared to results of previous studies[44, 45], which leaves less room for improvement on this outcome measure. Furthermore, the questions used to measure self-efficacy might not have covered the complete caregiver situation as they were focused on a few aspects of caregiving. Caregivers might feel that they are capable of fulfilling care tasks or dealing with upsetting thoughts about caregiving, but they might not feel in control over their caregiving situation in general.

Conclusion

The support program did not reduce distress although it might be beneficial in empowering caregivers by improving feelings of control in their difficult situation. Appropriate timing of this support program seems to be crucial for caregivers in order to complete the program and benefit from the content. Optimal timing may differ per individual and is likely dependent on multiple factors such as the disease phase of the patient, caregivers' needs, preferences, personal characteristics and their social network. It is recommended that information about the content of the program is provided early in the disease process and repeatedly thereafter.

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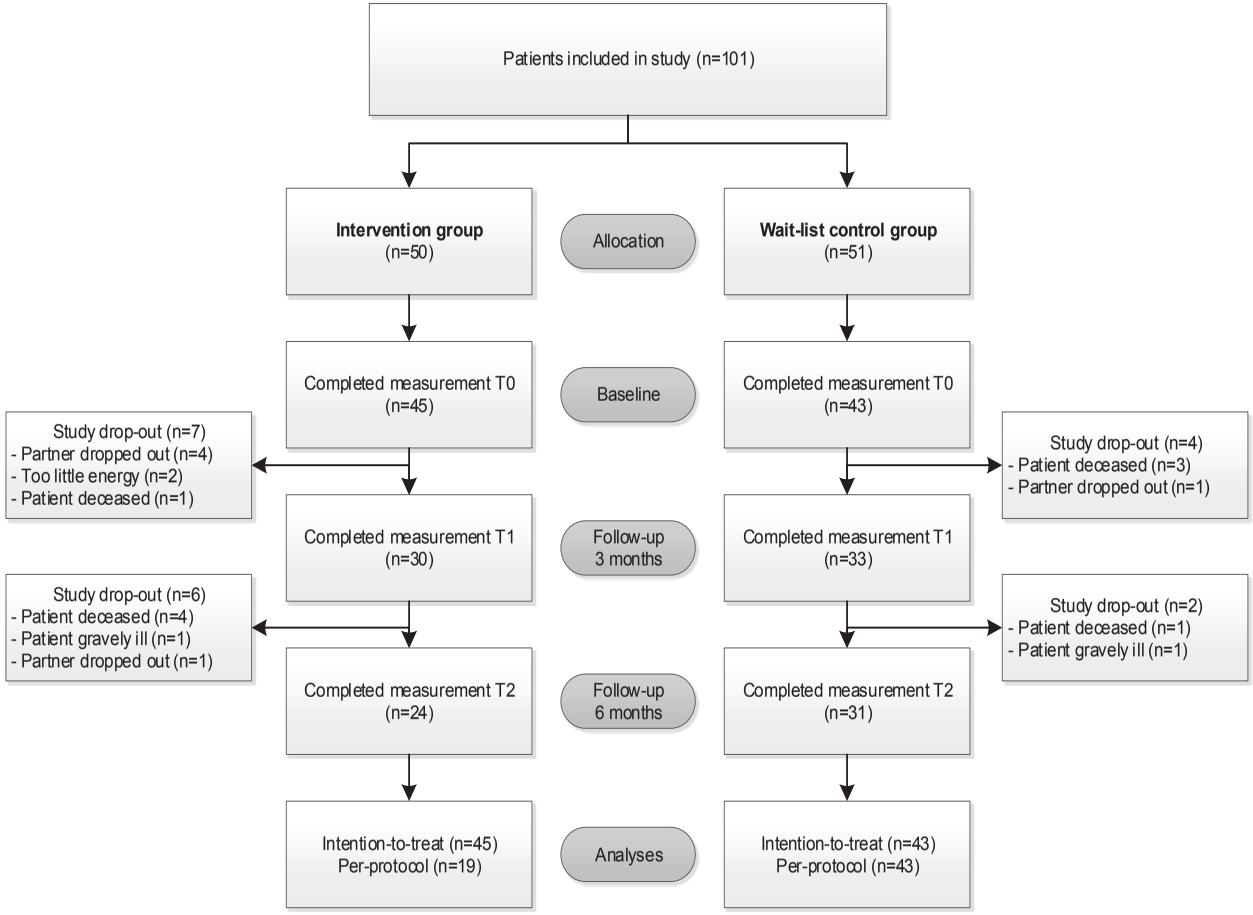
APPENDIX 1. Figure 2. Flowchart patients in study

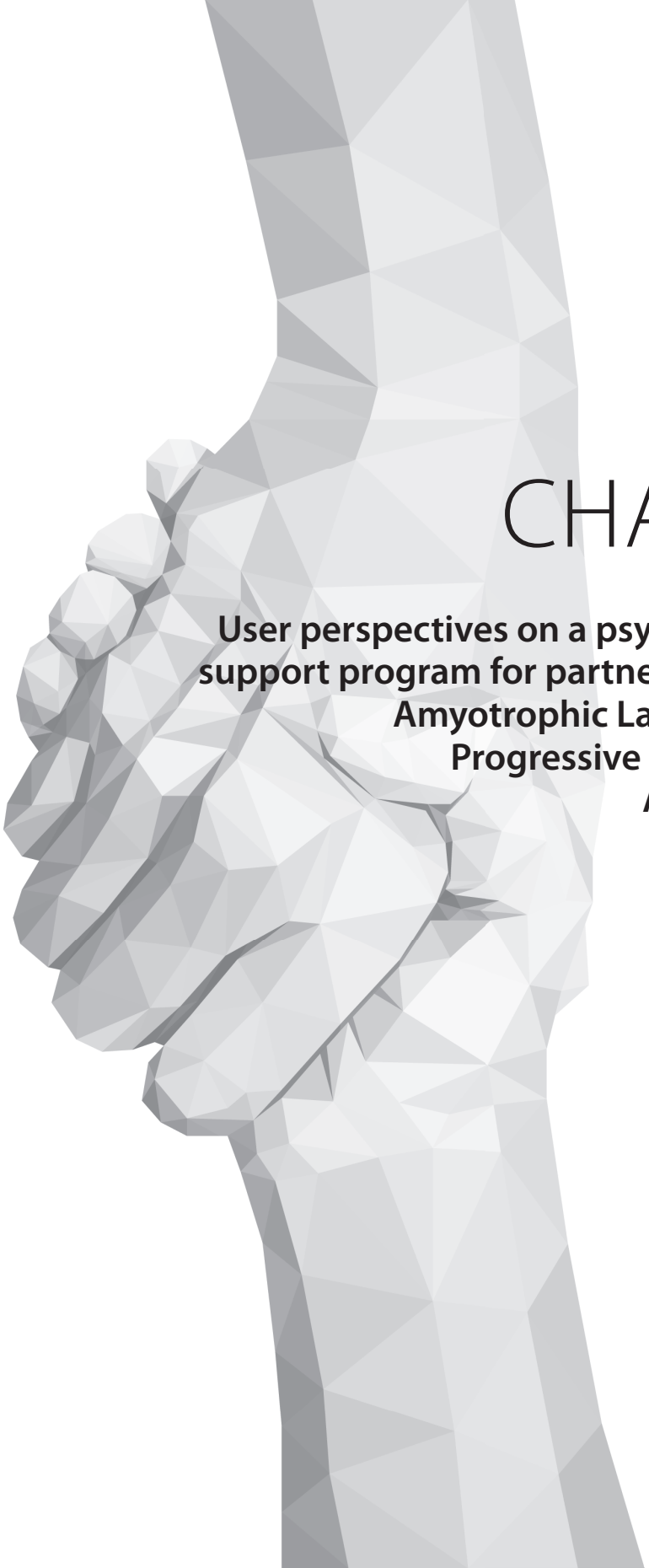


APPENDIX 2. CONSORT 2010 checklist of information to include when reporting a randomised trial

Section/Topic	Item No	Checklist item	Reported
Title and abstract			
	1a	Identification as a randomised trial in the title	YES
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	YES
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	YES
	2b	Specific objectives or hypotheses	YES
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	YES
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	YES
	4b	Settings and locations where the data were collected	YES
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	YES
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	YES
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	YES
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation			
Sequence generation	8a	Method used to generate the random allocation sequence	YES
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	YES
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	YES
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	YES
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	NA
	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	YES
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	YES
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	YES

APPENDIX 2. Continued

Section/Topic	Item No	Checklist item	Reported
	13b	For each group, losses and exclusions after randomisation, together with reasons	YES
Recruitment	14a	Dates defining the periods of recruitment and follow-up	YES
	14b	Why the trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	YES
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	YES
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	YES
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	NA
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	NA
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	YES
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	YES
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	YES
Other information			
Registration	23	Registration number and name of trial registry	YES
Protocol	24	Where the full trial protocol can be accessed, if available	YES
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	YES



CHAPTER 8

User perspectives on a psychosocial blended support program for partners of patients with Amyotrophic Lateral Sclerosis and Progressive Muscular Atrophy: A qualitative study

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BMC Psychology. 2019. In press

Abstract

Background: Partners are often the main caregivers in the care for patients with Amyotrophic Lateral Sclerosis (ALS) and Progressive Muscular Atrophy (PMA). Providing care during the progressive and fatal disease course of these patients is challenging and many caregivers experience feelings of distress. A blended psychosocial support program based on Acceptance and Commitment Therapy was developed to support partners of patients with ALS and PMA. The aim of this qualitative study is to gather insight into experiences with different components of the support program (program evaluation) and to discover what caregivers gained from following the program (mechanisms of impact).

Methods: Individual in-depth interviews, about caregivers' experiences with the support program were conducted with 23 caregivers of ALS/PMA patients enrolled in a randomized controlled trial designed to measure the effectiveness of the blended psychosocial support program. The program, performed under the guidance of a psychologist, consists of psychoeducation, psychological and mindfulness exercises, practical tips and information, and options for peer contact. Interviews were audio-recorded, transcribed verbatim and analyzed thematically.

Results: The program evaluation showed that caregivers perceived each component of the program as beneficial but ambivalent reactions were expressed about the mindfulness exercises and peer contact functions. Caregivers expressed the need for a more personalized program with respect to the order and timing of the modules and wanted to continue the support program for a longer time. The main mechanism of impact of the program that caregivers reported was that they became more aware of their own situation. They further indicated that the program helped them to perceive control over the caregiving situation, to accept negative emotions and thoughts, to be there for their partner and feel acknowledged.

Conclusions: The blended psychosocial support program for caregivers of patients with ALS/PMA is valued by caregivers for enhancing self-reflection on their challenging situation which stimulated them to make choices in line with their own needs and increased their feeling of control over caregiving. The different components of the program were overall appreciated by caregivers, but the mindfulness and peer support components should be further adapted to the needs of the caregivers.

Background

Caregivers of patients with Amyotrophic Lateral Sclerosis (ALS) or Progressive Muscular Atrophy (PMA) are confronted by many challenges during the progressive and fatal disease course of the patient. They are faced with physical deterioration and possible cognitive and behavioral changes in patients, which results in increasing demands on the caregiver.[1] Caregivers who experience increasing demand but do not feel in control over the caregiving situation are more likely to experience emotional distress according to the demand and control model.[2, 3] Research shows that caregivers experience high levels of distress and caregiver burden.[4, 5]

Although caregivers express a need for psychosocial support[6] supportive evidence based interventions for these caregivers are lacking.[7] A psychosocial support program was developed to diminish feelings of distress in caregivers of patients with ALS and PMA by enhancing caregivers' feelings of control over the caregiving situation.[8] The support program is based on Acceptance and Commitment Therapy (ACT).[9] ACT encourages individuals to accept unwanted private events which are out of personal control and to identify important values in life in order to pursue these values which might help caregivers of patients with ALS or PMA.[10] The program consists of a combination of face-to-face-, online- and telephonic contact (i.e. blended support). The content of the support program is originated from an existing intervention for partners of people with cancer[11] and adapted to the needs of caregivers of patients with ALS and PMA.

The effectiveness of the support program is currently being evaluated in a randomized controlled trial (RCT) in which caregiver-patient dyads are included. In order to understand the mechanisms of the impact of the intervention, a qualitative evaluation study regarding the experiences of caregivers with the support program, alongside the trial, is important.[12-14] Furthermore, insight into caregivers' experiences with the specific components of the intervention is valuable for implementation of care for these caregivers in the future.[14] Therefore, this study explores caregivers' experiences with a blended psychosocial support program for caregivers of patients with ALS/PMA. We aimed to gather insight into experiences with the different components of the program (program evaluation) and to discover what caregivers gained from following the support program (mechanisms of impact).

Methods

Study design

This qualitative study is embedded in an ongoing (RCT) investigating the effectiveness of the support program on psychological distress of caregivers (NTR5734). The protocol of the RCT is described in detail elsewhere.[8] The trial includes 148 caregivers and 88 patients.

The support program

The support program consists of an introductory face-to-face appointment with a psychologist, six psychologist-guided online modules and a concluding telephone contact with the psychologist (the content of the program is represented in Appendix 1). The face-to-face session was held at the residence of the caregiver. In this session, the psychologist explained the purpose of the intervention, received information about the caregiver's situation, demonstrated the online program and established a working relationship with the participant. After this session, the participant started with the first of 6 online modules. Every module was focused on a specific topic and consisted of different components (see table 1). After finishing a module, caregivers received feedback from the psychologist. The program ended with a telephone call in which the caregiver had the opportunity to ask advice or discuss their remaining questions. The program was scheduled to be completed within 8 weeks. However, if caregivers needed more time, this could be extended to 12 weeks. The support was provided by three psychologists who were trained to provide the intervention and who were not related to the multidisciplinary ALS care teams.

Sample and recruitment

Participants were purposively sampled from the 67 eligible caregivers in the RCT. Caregivers in the RCT met the following criteria: 1) the caregiver is the partner of the ALS or PMA patient; 2) the caregiver is 18 years or older; 3) the caregiver is proficient in Dutch to fill out the questionnaires; 4) the caregiver has internet access; 5) the caregiver has consent of the patient

Table 1. Content of each online module

Components
• *Psycho-education and exercises* Information directed at the theme of the module with psychological exercises based on ACT
• *Mindfulness exercises* Listening exercises to train conscious awareness and attention from one moment to the next moment
• *Practical information, tips and references* A list of relevant websites, organizations and other sources of information and support associated with the theme of the module
• *Contact with peers* 1. Sending private messages using a personal profile 2. Sharing tips and advice with regard to the topic of the module with fellow participants via a forum
• *Feedback of the psychologist* After finishing a module, the participant receives feedback on the completed exercises, a reflection on the progress and a reaction to any questions or difficulties via a text message

Abbreviations: ACT, Acceptance and Commitment Therapy

to participate, as the caregiver answers questions about the wellbeing of the patient. Caregivers in the RCT who completed or dropped out of the support program and who finished the third measurement (approximately 6 months after baseline), were selected. Only caregivers who completed the third measurement of the RCT were invited, as we did not want to influence the trial assessing the effectiveness of the intervention. Maximum variation in the sample was obtained by selecting caregivers with a wide distribution range with regard to age, gender and the physical and behavioral impairments of their partner. Selected caregivers were asked to participate via e-mail. In case of refusal, another caregiver was purposively sampled from the database as a replacement. In total, 40 caregivers were invited for an interview and 23 (57.5%) agreed to participate. Twelve caregivers did not respond to the invitation and five refused to participate. Reasons for refusal were: not willing to spend time on the study (1), afraid it would be too emotional (1), and having a partner in a critical phase of the disease (1). Two caregivers did not report a reason.

Data collection

Semi-structured interviews were conducted by telephone using an interview guideline. The interview guideline was developed with open questions related to caregivers' experiences with the support program in general, and the specific components of the program (Appendix 2). The interview guideline was peer reviewed by the research team and further refined during the iterative process and based on emerging themes. Participants who dropped out of the support program where interviewed about their reasons for dropping out and their experiences with the program. Caregivers who were interested in participating received the interview questions per e-mail as well as a summary of the content of the support program to help retrieve their memory of the intervention and to enhance reflection.

Interviews were conducted between June and September 2018 by a master student Health and Life Sciences who had been trained in conducting interviews (EE). The interviewer was not known to the participants prior to the start of the interview. All interviews were audiotaped. The duration of the interviews with caregivers who completed the support program ranged from 38 to 82 minutes (m = 57 minutes). Interviews with participants who had dropped out were shorter, ranging between 17 to 26 minutes in length (m = 22 minutes). During and directly after the interviews, memos were made to capture ideas about emerging themes and refinement of the interview guideline. Interviews were held until saturation was reached and confirmed during analysis of the last three interviews.[15]

Demographic characteristics of the caregivers and disease-related characteristics of the patients were gathered in the context of the RCT. Insight into the severity of the patient's disabilities was collected via the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R).[16] In this validated questionnaire, higher scores denote better physical functioning. Behavioral changes

in ALS or PMA patients were assessed using the Amyotrophic Lateral Sclerosis-Frontotemporal Dementia-Questionnaire (ALS-FTD-Q).[17] The validated questionnaire asks the caregiver to compare the patient's current behavior with his/her behavior 3 years ago and higher scores indicate more behavioral changes. Both questionnaires were completed by caregivers.

Data analysis

Interviews were analyzed thematically according to the six phases described by Braun and Clark.[18] The analytic steps and the roles of the authors in this process are presented in table 2. The data regarding the program evaluation were analyzed according to the first two steps. No in-depth thematic analyses were conducted on this data as we wanted to provide a description of the experiences with the different components. The software program NVIVO 10 was used to support data analysis.[19]

Table 2. Phases of thematic analysis according to Braun and Clarke

Phase	Description of process and role of authors
1. Familiarizing with the data	Interviews were transcribed verbatim and the accuracy of transcripts was checked by comparing the audio recordings with the transcripts (JW, EE). Transcripts were read and re-read by three authors (JW, EE, SV) and memos of initial ideas about themes and refinement of the interview guide were made and discussed (JW, EE, SV, CS). The authors had different professional backgrounds; i.a. psychology, nursing science and health sciences.
2. Generating initial codes	Transcripts were broken down into fragments based on content, and these fragments were labelled with codes by researchers independently (JW, EE). After every three interviews, results of their coding were compared and discrepancies discussed leading to consensus. A third researcher, who is an expert in qualitative research (SV), coded seven interviews. Results of the codes were discussed during meetings in which the researchers worked towards consensus about the coding and interpretations of the data (JW, EE, SV, CS).This approach established researchers' triangulation and increased the depth and credibility of the analysis.
3. Searching for themes	Codes were collated into potential themes whose relevance emerged across the interviews (JW, EE). A potential description of the main and subthemes was made. Potential themes were discussed in joint meetings (JW, EE, SV, CS).
4. Reviewing themes	Potential themes were reviewed for consistency with the codes and entire data to ensure they reflected the entire dataset (JW, EE). Inconsistencies were discussed and potential themes were further refined (JW, EE, SV, CS).
5. Defining and naming themes	The specific content of each theme was further worked out using the transcripts, and themes were named and defined (JW, EE, SV, CS).
6. Producing the report	Two researchers (JW, EE) wrote a first draft of the scientific report and selected quotes to illustrate themes. Two authors reviewed the report (CS, SV) and adjustments were made. This process was repeated until consensus was reached. The report was sent to the other members of the research team (AB, LB, JV) for critical assessment, and their feedback was processed.

The 15-point checklist of Braun and Clarke was used to confirm the correct application of the six phases of thematic analysis (Appendix 3).[18] Reporting in this paper is in accordance with the Standards for Reporting Qualitative Research (SRQR) checklist[20] (Appendix 4).

Results

The majority of participants were women (65%). The age of the caregivers ranged between 33 and 80 years (overall mean 59.6 years). Most patients were diagnosed with ALS (70 %). The personal characteristics of the caregivers and their patients are listed in table 3.

The results are presented in two main sections. The first section contains the program evaluation: user experiences with the different components of the program (table 1). Three important topics were added to provide a complete overview: 'receiving online support', 'timing of the intervention' and 'flexibility and length of the program'. The second section presents the themes regarding the mechanisms of impact (i.e. what caregivers gained from following the program) (see figure 1).

Table 3. Characteristics of interviewed partners

	Completers (*n*=17)	**Drop outs (*n*=6)**
Gender, n (%)		
Female	12 (70.6)	3 (50.0)
Male	5 (29.4)	3 (50.0)
Age in years, mean (SD)	59.9 (10.9)	58.7 (13.4)
Education level, n (%)		
Low	1 (6.0)	-
Medium	8 (47.0)	3 (50.0)
High	8 (47.0)	3 (50.0)
Diagnosis partner, n (%)		
ALS	13 (76.5)	3 (50.0)
PMA	4 (23.5)	3 (50.0)
Time since diagnosis in months, median	33 (9-253)	35 (12-82)
Parameters patient		
ALSFRS-R, median	25 (4-44)	24 (5-34)
ALS-FTD-Q, median	11 (0-38)	15.5 (8-33)

Abbreviations: ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; ALS-FTD-Q, Amyotrophic Lateral Sclerosis-Fronto Temporal Dementia-Questionnaire
Educational level: low = did not complete secondary school-completed low level secondary school; medium = completed medium level secondary school; high = completed upper level secondary school and/or university degree

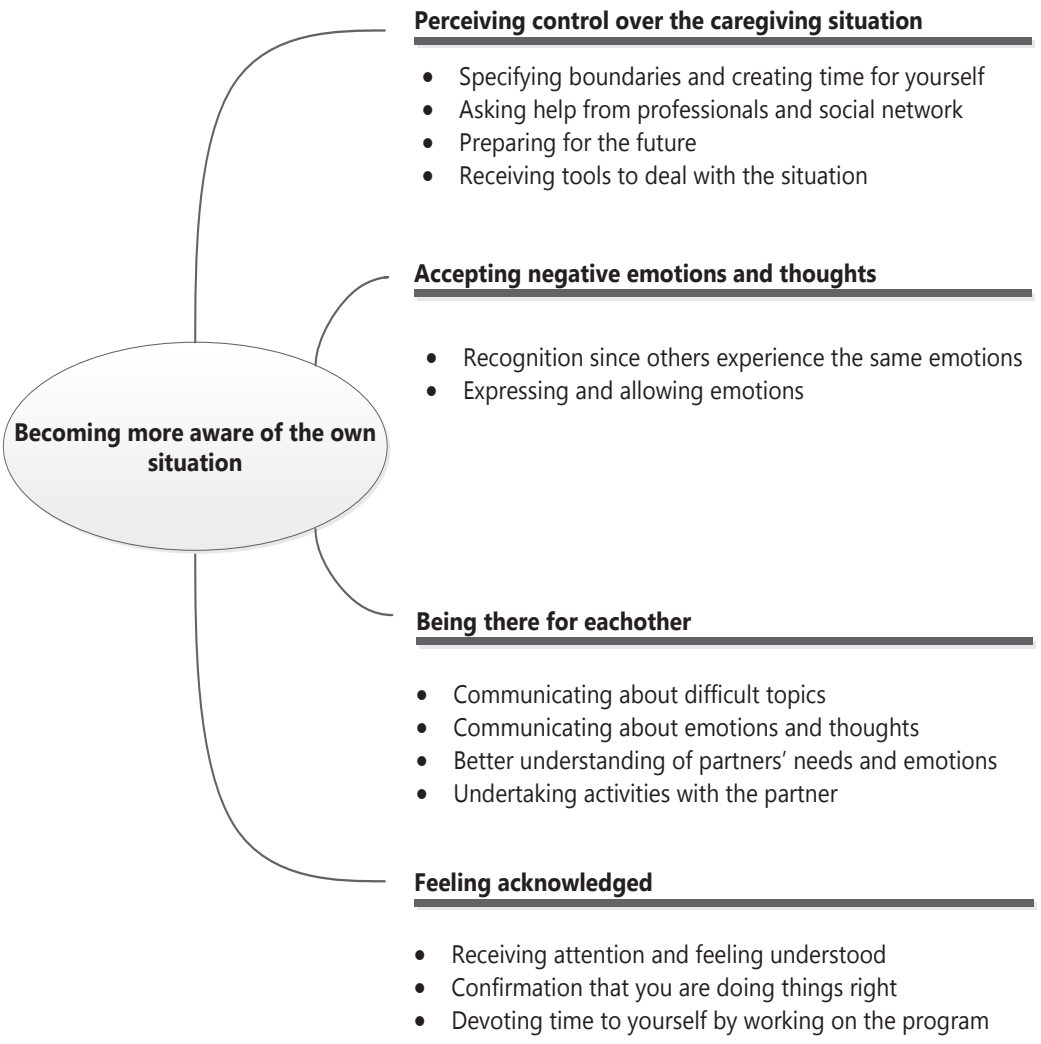

Figure 1. Overview themes and subthemes Mechanisms of impact

Program evaluation

In general, caregivers felt the program contained all the crucial themes relevant to their situation. Caregivers said there was coherence between the different modules, each module offering more in-depth information. The fact that the program contained disease-tailored themes and information was appreciated by caregivers:

"*I think it is very good that something like this exists, because my husband has the disease, but as a partner you will be dragged along with it. […] So I feel it's good that there is attention for that, and that you can receive some support for it. And yes of course it [the program] was very much related to the ALS disease. So it also deals very specifically with the course of that disease. So that really did help me.*" (*Respondent (R)5)*

Receiving support online

Most of the caregivers found the program easy to use and some mentioned that it had a user-friendly interface. The fact that each module had the same structure, and that each segment mentioned the time it would approximately take to complete it, was valued by caregivers.

There were some technical issues caregivers encountered, such as problems with saving the answers to the exercises or difficulties in leaving comments or tips for peers. These issues made some caregivers feel that the program was difficult to use. Some of them said they found computers in general difficult to use and were, therefore, struggling with the program:

"I encountered my lack of experience with these sorts of things [computers]. […] It's just that I don't know how to work with that." (R11)

By receiving the program online, it provided caregivers flexibility in pacing themselves, in contrast to traditional face-to-face support. The majority of caregivers appreciated the fact that they were able to work on the program whenever and wherever they wanted. They were also able to pause and continue with the program at any moment. Some valued this opportunity to think about the exercises and reflect upon their answers before submitting them. Being able to receive support at home was an important benefit of the program according to the caregivers. Some of them mentioned they would not have been able to receive support in a traditional care setting, such as via the specialized ALS team, because of their care responsibilities and the inability to leave their partner at home alone:

"I came to a point where I thought: I need something. Something that gives me air and makes me think. But then there's the problem you often face: I can't leave. […] The fact that it's online, it's a small step. It's different from conversations with someone, so it saves a lot of time. Online means you can do it at the moments that work for you." (R14)

Some caregivers would have preferred face-to-face support instead of online support. According to them, interaction via de computer lacks spontaneity and written answers come across differently due to the lack of verbal and non-verbal communication.

Timing of the intervention
The majority of caregivers perceived the timing of the intervention as appropriate and found the topics relevant in their situation:

"I think the program came at a good time. That everything is still relatively new for you, and can put your own things into perspective and that you receive support. Otherwise, you will keep going in circles for too long." (R17)

However, some caregivers of partners in a more advanced stage of the disease would have preferred to have received the intervention earlier. Receiving the intervention too late in the disease course was the main reason mentioned for dropping out of the program. A few felt the program did not offer them new information now, while it could have prepared them for what was to come had it been provided earlier. Others were so taken up by care tasks that they had limited time left for other activities. With little time available, some caregivers said the program started to feel burdensome:

"Usually I would do it [the program] almost at night, at the end of all the chores I have. And then I would start working on it, but it was just an extra chore added to my list. So I couldn't manage and I started falling behind etcetera and it started to become more of a burden than an aid." (Drop-out Respondent (DR)2)

Most caregivers of partners in the early disease stage found the intervention to be helpful as it pointed out what could happen in the future. However, some found that the intervention was not helpful to them yet as the need for support had not yet arisen and they preferred to spend time on other activities instead of focusing on the disease.

The subject, 'end of life', which is discussed in the last module, was difficult for many caregivers to read or discuss with their partner. Some caregivers did not want to follow the last module at all, skipped the exercises, or saved it to do it at a later moment when it would be more relevant.

Flexibility and length of the program
Caregivers appreciated the fact that exercises were not mandatory; they could freely choose which exercises they wanted to complete. This gave them the freedom to focus on elements that were relevant to their situation and to skip elements that were considered to be too confronting, not applicable, or not yet relevant. Some caregivers indicated that they would have preferred to

decide for themselves when they followed which modules, instead of following the modules in a fixed order. This would enable caregivers to select the modules most relevant to them at that moment. While the majority of caregivers felt there was sufficient time to complete the modules, some reported they would have liked to have more time in between modules to reflect upon the information received and to reduce the feeling of time pressure that some experienced.

Although most caregivers thought the length of the intervention was sufficient, caregivers expressed the desire to continue the intervention for a longer period of time or to have more follow-up appointments after the end of the program. Caregivers felt this would help them to retain the information longer and enhance the long-term effect of the program:

"Those 6 weeks, they really helped to sort things out again. But you gradually notice that you start to forget things. […] Things change so much with ALS. When I look at how I experienced it in the beginning and in the final phase, it is so different. So I would like to give it as advice to offer the program several times. It simply helps you to make conscious choices." (R14)

Psychoeducation and psychological exercises

Caregivers found the psycho-educational information in each module useful, as it offered a clear introduction to the theme of the module and it provided them with sufficient information to complete the exercises. Through the exercises, caregivers felt they received the tools to cope with difficult situations, emotions and negative thinking. Some caregivers indicated they had re-examined the information and exercises later on when they encountered issues related to these themes in their daily life.

"Sometimes I read or heard something and thought: 'I've had this in the modules, let's take a look'. And then I went back and looked at it [the psycho-educational information] and I found something there. So it was information I re-examined afterwards. I think that is positive, that you can look up information about situations you encounter." (R10)

Mindfulness exercises

The experiences with the mindfulness exercises were mixed. The majority of caregivers did not perceive the exercises as beneficial, and some caregivers said these led to adverse effects, including stress or feelings of restlessness. Finding the time to complete the mindfulness exercises was difficult for some caregivers. For others, the voice of the narrator was unpleasant or they found the text, that was read out, too woolly:

"I found the mindfulness, well, it just is not for me. That man that is speaking so unctuously, it made my hairs stand on end." (R7)

However, there were caregivers who did appreciate the mindfulness exercises. For them it was a valuable part of the program that provided them with a feeling of relaxation and calmness.

Practical information, tips and references
This component provided many caregivers with new links to relevant websites and information. One caregiver, for example, said this information helped her finally sort out an application for a personal care budget request. Caregivers felt that it provided a clear overview with useful and reliable information, as it had been developed by professionals in ALS:

"I found the information interesting and I've read it all. Before that, I thought, I'm not going on the Internet anymore. But then you think, this comes from the ALS Center, from professionals, I can read that. I have more faith in that, rather than the vague stories that you see on the Internet." (R12)

By saving this information on their computers, caregivers said, they were able to use the information provided later when needed. Other caregivers said they skipped this section because they did not have time to read it, or they felt it was too much to read at the end of a module.

Contact with peers
Caregivers could have contact with other caregivers in two ways: sending each other private messages or leaving tips and advice at a forum for others to read and react to. Caregivers who contacted others via direct messaging said this contact was valuable as it provided an opportunity to share their story and experiences. This one-on-one contact provided caregivers with recognition and acknowledgement: the notion that others were in the same situation, and that they had the right to feel the way they did:

"I have read pieces of text from other caregivers with tears in my eyes. Not because they are in a terrible situation but tears of joy of recognition. I can say straight away that that is the most important thing, because there you do see the recognition. In the outside world everyone goes on with their own lives, there you cannot find this recognition and acknowledgement." (R13)

However, most caregivers said that they did not feel the need to get in touch with peers through the program. For many, the threshold to contact someone via private messaging was too high, as they felt insufficiently informed about the situation of their fellow users. Some caregivers with a partner in an early disease stage felt no questions had yet arisen or felt it would be too confronting to talk to a peer caring for an ALS patient in a more advanced stage.

The tips and advice left by others were often considered to be too generic and therefore not useful. According to some caregivers, giving or receiving advice is not useful since each individual situation is different:

"There were tips from people in a much more advanced stage of the disease. […] That did not add anything for me. It is often about the life of someone else, I am not that interested in it and it doesn't offer me anything." (R12)

Others strongly valued the option to leave tips and advice for others as it gave them the opportunity to share experiences with others in a similar situation:

"Every week I left tips for others and I always read the tips from other participants. I found that one of the most fun parts of the program. I also considered that as very important. The reason for that may be that I did not encounter ALS in my personal environment, while I did feel the need to share experiences." (R14)

Contact with the counsellor and feedback

The majority of caregivers said they appreciated the home visit of the counsellor at the beginning of the support program and saw the home visit as an essential part of the support program. First, it provided caregivers with a face to go with the name of the counsellor. Second, the brief instructions given on how to use the program helped caregivers to get started. Third, caregivers felt that by seeing their situation, the counsellor was provided with context to the answers caregivers would send in and receive feedback on. As some caregivers indicated, this face-to-face meeting created a relationship of trust and understanding:

"It's nice to know who will be reading your things, and you would be more open than if you weren't to know who's behind it. I would have been more closed if I had not known who was on the other side." (R17)

Caregivers felt the contact with the counsellor was pleasant, as there was a short line of communication and caregivers felt comfortable asking the counsellor questions if necessary. Some caregivers mentioned that having a counsellor with knowledge on ALS was important, as they felt this provided the counsellor with a better understanding about the problems they might encounter as caregivers.

Many caregivers found the feedback on the exercises provided by the counsellor valuable because it helped them to reflect on their situation and offered them advice. The feedback confirmed the validity of their feelings and actions, which made them feel understood and encouraged. The majority of completers said they considered the feedback as a crucial part of the intervention, as it gave them insight into their own thoughts and feelings and it motivated caregivers to continue with the intervention. An important aspect of the feedback was that it applied to the caregivers' personal situation, and included elements of what they had filled in during the exercise. This made caregivers feel like they were listened to and that they were being taken seriously:

"She provided feedback and tips, and all in a very pleasant manner, like, 'oh think about this' […] It made me feel like a lot of care was put into it. That she really looked at it seriously." (R1)

However, others felt that the feedback was too brief and superficial. Their main objection was that the feedback was too recapitulatory: it summarised and repeated their answer back to them rather than providing them with new insights. As one caregiver illustrates.

"I think I wanted or hoped for more in-depth feedback. […] regarding the quality of the feedback I'd sometimes think hmmm." (R13)

Mechanisms of impact

Becoming more aware of the own situation

Caregivers became more aware of their own situation and reflected upon their situation through the support program. Due to the hectic and demanding care situation, caregivers were in a flow of providing care and as a result little attention was paid to self-reflection. The program encouraged caregivers to stand still and reflect, which they appreciated. The exercises required them to think about and describe their own situation in concrete terms. This forced caregivers to actively evaluate their current situation and to verbalize what they would like to see or do differently.

"I perceived the program as very useful because it made me think about what I want to do. I had to face the facts; how is it going right now? Are there things that I would like to do differently? That helped me." (R14)

In addition, the program offered new insights and perspectives, through the information provided and through the tips of other caregivers.

"I also got a bit of an idea of how other caregivers were looking at the care situation and what kind of other perspectives there are. I liked that. […] I realized, yes, it is also possible to see it in another perspective." (R9)

Perceiving control over the caregiving situation

Due to the program, caregivers reflected on their caregiving role now and in the future, the tasks they performed and the division between one's own time and caregiving. The program taught caregivers to recognise and set their personal boundaries. By indicating their boundaries, caregivers said they learned to keep control of their own life. One caregiver gave the example of cancelling work appointments because they were too demanding in terms of time and energy. The program helped caregivers to consciously think about the choices they were making and thereby define what was important to them. As another caregiver illustrates:

"What is really important? Well, you have to learn to discover that yourself and this (the program) helped with that. Like, you can also just say 'no'. Or you can tell your friends: 'you can't come to my house right now, I'll come to you.'" (R3)

The program also made caregivers aware that asking others for help could alleviate the demands that were placed on them and created more time for themselves. Asking for help from caregivers of professionals helped them to regain control over their situation.

"We do things more consciously and now also call in help from friends, family and neighbours. People offer help and ask whether they can do something for us. In the beginning we kept that off, but now we also ask people for help ourselves." (R12)

Caregivers felt that the assignments and themes covered in the program provided them with information to prepare for the future and provided them with tools to deal with future situations. Thereby, it gave caregivers more confidence in being able to handle the future and helped them accept the difficulty of what lies ahead:

"And if it comes, then you'll think: 'I've read this' , and it won't come as a surprise. I think that is much better, you have to be well prepared. And then it's easier to carry." (R10)

Accepting negative emotions and thoughts
Reflecting upon their situation provided caregivers insight into their thoughts and emotions. The intervention helped caregivers realize they were not alone in experiencing negative emotions and thoughts, and that these were valid to have in their difficult circumstances. This helped them to deal with these emotions and thoughts and caregivers felt they were able to accept this:

"[…] that you are not alone, that the feeling you have is right. Fears and other emotions that you have, that they are right and not different from others. Just the confirmation of this, and the description of the emotions and information in the modules. At the moment it made me more calm and I think that I am generally calmer now in respect to the disease." (R17)

Reading that these emotions and thoughts were normal in these circumstances also lowered the threshold for caregivers to express these emotions and thoughts.

"It became clear to me that I do not have to suppress my emotions. […] One of the things that has been confirmed was that you cannot help it [having these emotions] so you don't have to push them away." (DR3)

Being there for each other

The program made caregivers more aware about the relationship with their partner and the time they spent together. The program stimulated partners to think about the activities caregivers undertook with their partner. This made some caregivers decide they wanted to make changes, for example to spend more time with their partner:

"We gained from the program that we have more attention for each other. I sometimes play games and go to bed late, and now I'm trying to reduce that. And this has been successful. […] So we go to bed at the same time. I still use that. And that is something you become more aware of during the program." (R12)

Paying more attention to the spousal relationship also meant that caregivers were more inclined to share their emotions and thoughts with their partner. The program helped to enhance the communication with their partner as it encouraged caregivers to discuss topics with their partner in the exercises. Due to these exercises, caregivers communicated about their emotions and difficult subjects with their partner in a way they had not done before:

"[…] talking about the funeral, the preparations. That is something we don't discuss and we didn't discuss before. But because of the program, we have started talking about it." (R1)

Some couples jointly decided that they would start to talk about certain difficult topics such as life prolonging measures, when these would become relevant in their disease stage. Being on the same page with their partner with regard to these difficult topics made caregivers feel less stressed. Others felt the information in the program improved their understanding of their partner's needs and emotions. This increased understanding helped to improve the communication between them and their partner:

"I now recognize the reactions from my partner better and understand that she can experience different emotions and needs than I do. I now try to anticipate." (R9)

Feeling acknowledged

Caregivers were pleased to receive attention that was specifically intended for them: this made them feel heard and understood. It acknowledged that their role is important in the care process and reduced the feeling of being on their own.

"It has to do with the fact that it was aimed at me. That is what I enjoyed about it so much. The fact that I did something that was completely focused on me, that felt very nice." (R13)

Caregivers felt the information matched their situation well. Some of the strategies aimed at dealing with difficult situations and emotions introduced in the program were recognised by them as strategies they already applied in their daily lives. The intervention, therefore, endorsed that they were doing well in terms of, for example, discussing difficult subjects or planning quality time together. This confirmation gave caregivers a positive feeling and made them feel more self-confident about their coping strategies:

"I can remember that sometimes I would think: 'hey, I'm doing alright.' Cause there would be tips on how you could do things and they appealed to me and they supported me in a sense that I already did those things myself or already thought about that way." (DR4)

By participating in the support program, caregivers had to spend time on reading and completing exercises. Some caregivers rarely sat down and took time for themselves and they experienced this as a positive effect of the support program.

"[…] that you had to take time for yourself. […] that you're more or less forced to sit down calmly and to think about things for a bit. That worked for me." (R5)

Discussion

Caregivers evaluated the support program positively. They indicated that the support program increased their awareness with regard to their own situation. Having a partner who received a diagnosis of ALS or PMA is experienced as a highly demanding and overwhelming situation.[21] Reflecting on their current situation and their role therein does not seem self-evident for caregivers who are in the constant flow of providing care. The program 'forced' caregivers to reflect on and become more aware of their situation which was considered as a crucial function of the program by caregivers. Becoming aware of your own situation is one of the first stages that people go through during the process of change that takes place in psychological therapy.[22] In the stages that follow, people modify their behavior, experiences, and environment to overcome difficulties.[22] Becoming more aware of their own situation made caregivers in the current study realize they wanted or needed to do things differently in order to remain healthy.

Due to the program, caregivers perceived more control over their care situation, accepted negative emotions and thoughts, reported increased attention to their partner relationship and felt acknowledged. The program empowered caregivers to make choices according to their own needs which they perceived as a positive change. This is in line with the rationale of the demand and control model, in which increased perceived feelings of control act as a protective buffer against the impact of perceived demands on the wellbeing of the caregiver.[3] Furthermore, previous

research has shown that accepting negative emotions and thoughts has positive effects on the wellbeing of individuals.[23] Our study showed that this is also beneficial for the partner relationship; caregivers became more aware of their emotions and thoughts and talked about these topics with their spouse. It has been demonstrated that sharing emotions and thoughts and communicating about disease-related topics with your partner leads to increased feelings of intimacy[24-26], while hiding worries and dismissing negative emotions are associated with more perceived distress.[27, 28]

Caregivers are often inclined to neglect their own needs and wellbeing.[6] Our study revealed that caregivers appreciated a support program specifically aimed at them because the attention from professionals and the social network is mostly focused on the patient.[29] This indicates that there is an unmet underlying need for support. Providing support online may lower the threshold to accept support for these caregivers.

Caregivers in this study valued the online support because they were able to enter the program at their preferred time and place, and could work on the program at their own pace. These benefits were also reported in other studies for caregivers.[30-32] Since these caregivers are often occupied with care tasks which makes it complicated to receive face-to-face support, using online support seems to be a suitable way to provide support and to reach out to the caregivers who are in need of care.[33]

Overall, the different components of the support program were appreciated by the caregivers, but they expressed mixed opinions regarding the components mindfulness and peer support. Although mindfulness based interventions has been shown to decrease feelings of depression and caregiver burden in caregivers[34, 35], most caregivers in our study did not perceive the mindfulness exercises as helpful. Yet, it is not uncommon for participants to report unpleasant reactions, such as agitation, discomfort, or confusion during mindfulness interventions.[36] These reactions are viewed as part of the psychological process, since mindful attention to one's reactions is thought to help participants explore and understand these reactions.[36] Providing more information and support with regard to this process might be needed. Another important remark here is that caregivers, who perceived the mindfulness exercises as helpful, were those with prior experience with mindfulness of meditation.

The other component that received mixed evaluations was the option of peer contact. The majority of the caregivers mentioned that they were not in need of peer contact or they thought talking to others in a more advanced stage would be too confronting. These results are in line with the results in previous studies, which concluded that the fear of negative prospects can prevent participants from seeking peer contact.[37, 38] Although peer support can have advantages, having contact with others who are coping well can provide hope and generate information which positively impacts upon one's own problem solving skills.[38, 39] But it might not be suitable

for everyone. Providing mindfulness and peer contact as optional parts of the support program is recommended for future implementation.

Clinical implications

Caregivers stressed that the timing of interventions should match their needs for them to perceive the intervention as helpful. However, the right timing for a support intervention might differ for each individual caregiver. In addition, the needs of caregivers change during the disease course[40] and they seem to be reluctant to seek support for themselves.[41] Acknowledging the important role of these caregivers in the care of patients at an early stage and underlining their risk of psychological distress by care professionals, are crucial to lowering the boundaries for caregivers to accept the support offered. Receiving interventions early in the disease trajectory may better prepare caregivers for what is yet to come and provide them with tools in order to prevent caregiver distress in the future. For caregivers of patients in a more advanced stage of the disease, receiving support is difficult, as they might not have enough time to spent on support or they may no longer be able to benefit from it due to the progressed disease stage. Therefore, it is recommended that information about the support program, as well as other supportive interventions by the multidisciplinary ALS care teams, is provided in an early phase of the disease and repeatedly thereafter.[33]

Another way of making care more accessible is by providing personalized support where caregivers can choose options. In case of the support program, following modules in a self-chosen order and time may increase the perceived acceptability and value of the intervention. This is in line with the current focus in the field of caregiver interventions; targeting interventions to specific caregiving groups and subsequently tailoring those to individual caregiver's needs.[42] Offering tailored interventions according to the needs of the recipient reduces negative effects of interventions, decreases waste of time and effort of both recipient and professional, and may increase the compliance with the intervention.[43]

Strengths

This study was nested within a RCT and may provide information that enhances the understanding of the results of the trial and the implementation once the effectiveness has been established. To strengthen the trustworthiness of the study, data were independently analysed by two researchers and supported by a qualitative research expert during the process of analysis. Memo writing, the use of the checklist of Braun & Clark and the SRQR checklist further enhanced the trustworthiness.[18, 20] Furthermore, the interviewer was unknown to the participants prior to the interview and was not part of the trial, which might have positively affected the representativeness of the results.

Limitations

A few limitations need to be considered. First, interviews were conducted after completing the intervention and this retrograde reflection might not have revealed all experiences with the intervention. Second, there was a delay between completing the intervention and the interview, which might have affected caregivers' memory to recall the details of the intervention. Therefore, a short summary of all modules of the intervention was provided a few days before the interview to help retrieve caregivers' memory. A third limitation is that the interviews were conducted by telephone for logistic reasons. Face-to-face interviews could have encouraged caregivers to further elaborate on their answers which may have enriched the data.[44] However, telephonic interviews may allow respondents to disclose sensitive information more freely.[45]

Conclusion

Partners of patients with ALS and PMA overall appreciated the blended psychosocial support program based on ACT but they expressed mixed feelings about the mindfulness and peer support components. The program increased their awareness with regard to their own situation; increased their perceived control over the care situation; helped to accept negative emotions and thoughts; increased their attention for their partner relationship and acknowledged them. Our program should be considered as a complementary approach to multidisciplinary ALS care in which the important role of these caregivers and their risk of distress and burden are acknowledged. Offering interventions by the ALS care team early in the disease course and repeatedly thereafter is preferable, as care needs change over time. Providing information about the content of the program and subsequently tailoring the program to the specific needs of the caregivers (i.e. caregivers choose which module at what time and which pace) may increase the perceived benefits and compliance with the intervention.

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APPENDIX 1. Content intervention

Part of intervention	Topics	Goals	Key components
Face-to-face session	• The care situation • Wellbeing caregiver • Information about support program • Log in online modules	To receive information about the care situation and establish a relationship between the psychologist and the caregiver. To inform about caregiver burden and start online modules.	• Psychoeducation
Online module 1 Coping with your emotions and thoughts	• Dealing with and expressing emotions • Recognizing thoughts	To recognize emotions and encourage caregivers to allow, express and share emotions that can arise. To recognize dysfunctional thoughts and rumination. Change the way the caregiver relates to thoughts/ to create distance from thoughts.	• Acceptance • Cognitive defusion • Mindfulness
Online module 2 The art of communication	• Communication style • Communicating about sensitive topics • Communication about providing care	To improve the overall communication and to communicate with the patient about sensitive topics and providing care in the future.	• Communicating about what really matters • Mindfulness
Online module 3 Your resilience plan	• Dealing with continuous stress • Moments of relaxation • Using your sources	To make a resilience plan that may allow caregivers to maintain health during this stressful period by taking care of themselves.	• Acceptance • Mindfulness
Online module 4 What is really important	• Values in relationship • Values in life	To identify the values of the caregiver in different areas of life and to plan actions to meet these values.	• Values • Commited action • Mindfulness
Online module 5 Moments of joy	• Positivity during difficult times • Celebrate the relationship	To seek, enjoy and cherish the positive moments in the relationship and in life.	• Committed action • Mindfulness
Online module 6 A good last period	• Life story of the patient • Communication in this last phase • Beautiful memories • Being grateful	To create a beautiful last period with the loved ones and to make memories with the patient for the future.	• Acceptance • Communicating about what really matters • Committed action • Mindfulness
Telephone call	• Any questions • Finish the support program	To offer support with regard to any issues and close the support program.	

APPENDIX 2. Interview guidelines

Topics interviews with completers

- Experiences with the program in general
- Motivation to start with the program
- Perceived benefits of the program
- Perceived disadvantages of the program
- Match of the program with the needs of the caregiver
- Timing of the program
- Structure of the program
- Receiving online support
- Experiences with the different components of the program:
    - Home visit
    - Psychoeducation
    - Psychological exercises
    - Mindfulness
    - Information, tips and references
    - Contact with peers
    - Feedback from the counselor
    - Contact with the counselor

Topics interviews with drop out

- Reasons for dropping out
- Expectations of the program before the start
- Perceived benefits of the program
- Perceived disadvantages of the program
- Elements that could have prevented dropping out

APPENDIX 3. Checklist Criteria for Good Thematic Analysis: 15-pointchecklist

Process	Criteria	Reported
Transcription	1. The data have been transcribed with an appropriate level of detail, and the transcripts have been checked against the tapes for 'accuracy'.	YES
Coding	2. Each data item has been given equal attention in the coding process.	YES
	3. Themes have not been generated from a few vivid examples (an anecdotal approach), but instead the coding process has been thorough, inclusive and comprehensive.	YES
	4. All relevant extracts for each theme have been collated.	YES
	5. Themes have been checked against each other and against the original data set.	YES
	6. Themes are internally coherent, consistent, and distinctive.	YES
Analysis	7. Data have been analysed – interpreted, made sense of - rather than just paraphrased or described.	YES
	8. Analysis and data match each other – the extracts illustrate the analytical claims.	YES
	9. Analysis tells a convincing and well-organised story about the data and topic.	YES
	10. A good balance between analytical narrative and illustrative extracts is provided.	YES
Overall	11. Enough time has been allocated to complete all phases of the analysis adequately, without rushing a phase or giving it a once-over-lightly.	YES
Written report	12. The assumptions about, and specific approach to, thematic analysis are clearly explicated.	YES
	13. There is a good fit between what you claim you do, and what you show you have done – i.e., described method and reported analysis are consistent.	YES
	14. The language and concepts used in the report are consistent with the epistemological position of the analysis.	YES
	15. The researcher is positioned as active in the research process; themes do not just 'emerge'.	YES

CHAPTER 9

General discussion

The overall aim of this thesis is to improve the support for caregivers of people with ALS or PMA in order to enhance their wellbeing. The subaims of this thesis are:

1. To unravel which caregiver and patient factors are related to caregiver burden and psychological distress in caregivers of people with ALS or PMA.
2. To increase knowledge about the support needs of caregivers of people with ALS or PMA.
3. To develop a blended support program for caregivers of people with ALS or PMA and evaluate the support program both quantitative and qualitative.

In this chapter we reflect on the main findings and provide recommendations for clinical practice and future research.

1. Factors related to caregiver burden and psychological distress

Main findings

- Chapter 2 revealed that higher caregiver burden was associated with greater behavioral and physical impairment of the patient and with more depressive feelings of the caregiver. A lack of research focusing on the personal factors of the caregiver was identified.
- Chapter 3 showed that psychological distress increases over a period of 10 months in caregivers. Only emotion-oriented coping was related to psychological distress but emotional coping and psychological distress may represent overlapping constructs. Focusing on one coping style in the care for patients with ALS seems to be too simplistic for the complex situations they face.
- Chapter 4 showed that the presence of more behavioral changes in the patient and lower perceived control over caregiving were associated with higher levels of psychological distress in caregivers. Physical impairments of the patients were not related with psychological distress in caregivers. Perceived control did not influence or determine the relationship between physical impairments or behavioral changes and psychological distress.

Reflection

The studies in this thesis show that physical functioning of the patient is significantly related to caregiver burden but not to psychological distress.[1, 2] The concepts caregiver burden and psychological distress are frequently used interchangeably as if they represent the same construct.[3] This research underlines that a distinction between these constructs should be made. Although caregiver burden and psychological distress are related, they do represent different constructs.[1, 4, 5] Caregiver burden is a broader construct and is defined as the impact on the emotional health, physical health, social life and the financial status of the caregiver as a result of adopting the caregiving role[6] and contains objective and subjective aspects. Objective burden

represents the tasks required of caregivers and time spent on caregiving. Subjective burden characterizes the perceived impact of the objective burden and caregivers' own perception of their caregiving roles.[7, 8] Psychological distress is defined as a discomforting, emotional state in response to a stressor[9] and is often operationalized as symptoms of anxiety and depression.[10] When these constructs are measured with questionnaires, both questionnaires can include questions related to depressive feelings ("Do you feel tired and worn out?" Caregiver Burden Scale item 1; " I feel as if I am slowed down" Hospital Anxiety and Depression Scale item 8).[10, 11] However, caregiver burden scales often contain questions about both the objective care situation and the subjective experience of the situation. Questionnaires including questions about the objective care situation might insinuate that caregivers experience a high amount of burden, while in reality this might not be how caregivers perceive their situation. Caregiver burden scales are a good starting point for a conversation in daily practice, as it provides insight into the caregiver situation. However, concluding that a caregiver is psychologically distressed based on a caregiver burden questionnaire is not recommended. Despite the fact that the objective care situation seems burdensome, caregivers can find benefit through caregiving.[12] Examples of positive aspects of caregiving in caregivers of patients with ALS include strengthening relationships, increasing self-trust, focusing on simple pleasures and learning to see things from a different point of view.[13,14] Benefit finding has been found to be associated with lower levels of depressive symptoms in caregivers of patients with ALS.[12]

The presence of behavioral changes in patients (e.g. apathy, abnormal behaviour, stereotypical and motor behaviours, changes in eating habits) is related to psychological distress and caregiver burden, while the physical functioning of the patient is only associated with caregiver burden.[1, 2] The fact that psychological distress is not associated with patients' physical functioning may come as a surprise since ALS and PMA are diseases that severely impact the physical functioning and make patients completely dependent on their environment.[15] The different effects of physical and behavioral impairments on psychological distress might be related to the consequences on the care situation. Patients who experience physical complaints are able to receive professional support. In the Netherlands the health care system is well organized in providing support for problems in physical functioning.[16] However, in patients with behavioral problems the behaviour can be unpredictable and receiving informal or professional support to deal with the situation and consequences is more complicated. Dealing with behavioral changes might require emotional adjustments and caregivers have reported that health care services place disproportionate focus on the practical rather than emotional adjustments to the disease.[17] Moreover, caregivers who are able to discuss problems with patients and feel supported by them deal better with the consequences of the disease and show lower levels of distress.[18, 19] In patients with behavioral problems, receiving support and solving problems jointly might be more difficult and this may have a strong impact on their relationship and the wellbeing of the caregiver. Living with a patient who shows behavioral changes might therefore be more stressful and may lead to

feelings of psychological distress. In caregivers of patients with (frontotemporal) dementia and stroke, behavioral problems have also shown to be related to caregiver burden and psychological distress.[20, 21]

The results of this thesis underline that physical disabilities of the patient and its effects on the caregiver should not be the only focus of professionals who provide support to families with ALS or PMA. Providing information about the cognitive and behavioral functioning of patients is important in order to deal with these symptoms for both patients and caregivers.[22, 23] Caregivers are often not fully informed about the cognitive and behavioral differences that can occur due to the disease.[24] For caregivers it is often unclear why patients behave differently and they cannot get a grip on the situation.[25] For example, apathy which is the most common behavior change, comprises a lack of motivation and quantitative reduction of voluntary behaviors.[26] Caregivers find it difficult to deal with this behavior because they feel like they have limited time left and they would like to undertake activities together.[25] Caregivers may interpret patients' symptoms as consequences of a depression followed by the diagnosis, while research shows that anxiety and depression are not related to behavioral symptoms including apathy.[27, 28] Providing education about possible behavioral and cognitive changes that might accompany the patients disability is therefore important.[29] The prevalence of cognitive and behavioral changes is high in patients with ALS and PMA since up to 50% of the patients show these changes.[30-32] This emphasizes the relevance of monitoring these symptoms and making a distinction in diagnosis between pure ALS or PMA, ALSFTD, ALS/PMA with cognitive problems or ALS/PMA with behavioral problems.[33] However, the main focus should not only be on diagnosing patients with cognitive of behavioral problems. More important is to implicate these findings in the support for both patients and caregiver and to provide support in how to handle difficult situations. Currently, this type of support is often not provided in the care for patients with ALS or PMA.[23] Interventions aimed at dealing with behavioral changes in patients with (frontotemporal) dementia using psychoeducation and teaching caregivers new coping strategies, have shown promising results.[34, 35]

The demand and control model provides a way to explain psychological distress perceived by caregivers.[36] This model could help professionals to explain the risks of distress to caregivers and may encourage talking about feelings of distress. However, measuring the demand and control dimensions has shown to be complicated. Although the model partly explains the variety of distress in caregivers when demand is operationalized as behavioral changes and control is operationalized as feeling in control over caregiving, the majority of the variance in distress is still unexplained.[2] We targeted the demand and control model from a medical perspective, looking at the physical and behavioral demands and completing caregiving tasks, while in fact more factors are involved. Factors that might have influenced the perceived demand and control in caregivers; such as social support[37], the quality of the partner relationship[38] and professional support[39] were not included in the model. What we learned from the demand and control model in combination

with the results of our research is that we need to shift the focus from the patient and the effects of the disease on the patient's functioning to the caregiver and how they deal with difficult situations and whether they feel in control over their situation. Especially in a progressive and incurable disease, the demand will increase and this can not be influenced. Therefore, we should pay more attention on strengthening the caregivers in order to deal with their complex situation. Identifying the strengths of the caregiver, and how their feeling of control can be enforced could help caregivers feel more confident and in control in their situation, which in turn leads to lower levels of psychological distress.[36] Addressing the strengths of the caregiver is a first step towards family-centred care, in which the strengths and needs of all family members are considered throughout all phases of the rehabilitation process.[40, 41]

2. Support needs of caregivers

Main findings

- Chapter 5 showed that caregivers experience four global support needs: 'more personal time', 'assistance in applying for resources', 'counseling', and 'peer contact'. Despite their need for support, caregivers are reluctant to seek or accept support for themselves. Their main priority is taking care of the patient.

Reflection

Our research showed that there are strong differences between caregivers with regard to their needs.[25] Additionally, needs differ in caregivers over time and are influenced by the disease stage of the patient and the personal characteristics of the caregiver.[25, 42] Therefore, being attentive to and addressing the needs of caregivers is important during the whole disease course of the patient. However, caregivers often do not express their needs and put the patient's needs before their own[25, 43], which is in accordance with earlier studies in caregivers of patients with life threatening illnesses.[44, 45] Caregivers are focused on the temporariness of the situation and expect the illness trajectory to be short; they are willing to put their life on hold to provide care.[46] Since the disease length is often unclear and can be prolonged by life-lengthening technology, this can lead to high levels of distress.[47] Highlighting the importance of the wellbeing of the caregiver by professionals is crucial in order to lower the boundaries for caregivers to accept support.[43] Repeatedly talking with caregivers about their needs is therefore crucial for professionals in order to provide adequate support.[48] Providing attention by questioning needs and offering support to caregivers in itself may have beneficial effects on caregivers, since perceived lack of support is related to decreased caregiver wellbeing.[39] Since needs of caregivers may vary largely, a range of support services seems to be required to meet these needs.[48, 49]

The fact that ALS and PMA are unpredictable, variable and progressive diseases makes caregiving even more challenging. The struggle with uncertainty and continuously being confronted with new and unknown problems as the condition unfolds, may make it difficult for caregivers to maintain a sense of control over their situation. They are faced with new situations without having the acquired knowledge or skills to deal with the stressors.[48] The feeling of having lost control over the situation can be expressed by caregivers in a wide range of questions for practical support. Therefore, it is important that health professionals not only pay attention to the individual questions but also support them to regain perceived control over the whole caregiving situation.

3. A blended support program: ALS caregiver support

Main findings

- Chapter 7 presents the results of the randomized control trial that evaluated the effectiveness of the support program described in chapter 6. Although caregivers evaluated the program positively, no significant differences between the intervention group and wait-list control group on psychological distress, caregiver burden or quality of life in caregivers, nor on quality of life or psychological distress in patients was found. A significant positive intervention effect was found on the intervening variable self-efficacy with regard to being in control over thoughts. Almost half of the caregivers did not complete the intervention.
- Chapter 8 showed that caregivers perceived each component of the program as beneficial but ambivalent reactions were expressed about the mindfulness exercises and peer contact functions. The main mechanism of impact of the program that caregivers reported was that they became more aware of their own situation. The program helped them to perceive control over the caregiving situation, to accept negative emotions and thoughts, to be there for their partner and feel acknowledged. The need for a more personalized program was expressed.

Reflection

Although the RCT showed that the program did not lead to decreases in the psychological distress, caregiver burden or quality of life in caregivers, nor to reduced quality of life or psychological distress in patients, the qualitative study showed that caregivers appreciated the support program.[50, 51] The mixed method design provided more insight into the working mechanisms of the intervention and showed that caregivers benefited in different ways of the program.[50] A significant positive intervention effect was found on the intervening variable self-efficacy with regard to being in control over thoughts[51] and caregivers expressed they perceived more control over their caregiving situation.[50] This increase in control and the acceptance of negative emotions and thoughts, the focus on the partner relationship and the feeling of being acknowledged might have helped caregivers in dealing with their situation.

Results of these studies also showed that the timing of the intervention was crucial.[50, 51] The aim of the program was to offer a support program for caregivers in order to diminish the increase of feelings of distress over time. The support program should therefore be offered early in the disease process in order to equip caregivers with tools they can use in challenging caregiving situations to remain a feeling of control over their caregiving situation. However, providing preventive interventions is challenging because caregivers in the early stages of the disease may not experience problems and are therefore not interested in receiving support. In addition, caregivers do not prefer to be confronted with the more advanced stages of the disease and caregivers who do experience problems may become overwhelmed and may not feel they have any mental space left to receive support.[52] Therefore, the timing of an intervention is crucial but also complex, caregivers need to recognize that the support program can be beneficial for them. Therefore, informing caregivers proactively early in the disease stage about the support options and repeatedly thereafter may increase the uptake of support and prevent high levels of distress.[53] Health professionals play an important role in the uptake of interventions by motivating people and providing them with information and referral.[54, 55]

One size does not fit all; our research showed that one type of program that is offered to every caregiver at any disease stage does not fit to the needs of all the caregivers. Although caregivers could extract the information from the program that is applicable to their own situation, a better match between the needs and content for the support seems to be important in order to feel optimally supported. In line with personalized medicine, tailored support for each unique caregiver situation is needed. Offering caregivers a choice in when to start support and which topic is important to them is likely to increase the perceived benefit of the program.[56] This program can be one of the support options offered to caregivers.

One of the main benefits of the program, was that caregivers could follow the program when and wherever they wanted due to the use of e-health.[50] For partners who are involved in caregiving it can be difficult to receive professional support at a care facility, because they do not want to leave the patient alone. E-health is a comfortable and accessible way to receive support and it lowers boundaries to accept support.[57] Providing blended support has shown to be beneficial; professionals can introduce users into the program and the user perceives the approach as personal and appreciates to know who is providing support. However, for some caregivers using the computer was still complex, therefore, it should not be the only way of support, but an option next to the traditional face-to-face care. One of the challenges in using e-health within the usual care is the implementation.[58] Research shows that many factors influence the process of successful implementation of e-health: the e-health technology, policies and incentives, the compatibility of the organization, individual health professionals and the process of implementation.[59] These factors are also the challenges we face in the implementation of this support program; the organization of the current care system is not fully ready to easily adopt an e-health intervention.

In order to reach out to caregivers outside the standard care system, the support program could be offered openly through a website. This may increase the accessibility for those caregivers who are motivated to receive support with regard to their caregiving situation but who do not receive support from an ALS care team or who would like to receive support outside of the ALS care team. Providing support outside of the standard care could also lower boundaries for caregivers to seek support. However, in order to cover (a part of) the hosting costs and the costs for professional guidance, a financial contribution might be needed from participants.

Clinical recommendations

Caregivers play a critical role in the care of patients with ALS or PMA. Their wellbeing is important, not only for their own health but also for the health of patients. These caregivers enable patients to remain at home during the course of the disease. To improve the support for these caregivers, ten clinical recommendation were formulated based on the information gathered in this thesis.

1. *Acknowledge caregivers and standardize the provision of support for caregivers*
   Caregivers often see their own wellbeing as subordinate to the wellbeing of the patient. Since they have a major role in caregiving, acknowledging the importance of their role and their wellbeing is important. Psychoeducation about the development of feelings of distress over time in caregivers in general can make caregivers more aware about their own wellbeing. Acknowledge that people experience many emotions and thoughts during the course of the disease. Acknowledging that this situation can be challenging lowers the boundary to ask support from people in their personal environment or from professionals. Providing support to caregivers needs to be standard in ALS care. Further integration of caregiver support in all facets of the care system is needed in order to make caregiver support a standardized part of the care for patients with ALS or PMA. Options for caregiver support should be integrated in information brochures and websites available for patients and informal caregivers. Furthermore, caregiver support should be embedded more explicitly in the clinical training of health care professionals and in the curricula of health care students.

2. *Be careful with the use of the Dutch word for 'caregiver' [mantelzorger]*
   Family members or friends who provide support for patients with ALS or PMA do often not experience themselves as caregivers. Partners who provided feedback on our texts in our studies disliked the word 'mantelzorger'. They felt they were looking after the patient because they loved the person and they wanted to help him/her, just like before the disease and just like he/she would do for them. The word 'mantelzorger' did not suit that description. The use of the word 'mantelzorger' should, therefore, be used cautiously in the communication with the caregivers. Caregivers might nog feel addressed by this word and might as a consequence miss out on support.

3. *Make time to see the caregiver privately*
   Caregivers often find it difficult to speak openly about their situation in the presence of the patient. Caregivers say they feel like they betray the patient when they talk negatively about the care situation or about the behavior of the patient. When professionals make time to talk to caregivers privately, caregivers feel more free to ask questions or advice with regard to the care situation or the patient.

4. *Actively ask caregivers about their needs*
   Explicit attention for the needs of caregivers is important in order to provide support. Caregivers might not experience feelings of burden of distress, but they might experience a need for support. Paying attention to their needs might prevent high levels of caregiver burden and psychological distress.

5. *Monitor the wellbeing of caregivers*
   Monitoring the wellbeing of each individual caregiver by the multidisciplinary ALS care team is important in order to intervene when necessary. Caregivers experience increasing amounts of psychological distress over time. But there is also strong diversity between the development of distress in different caregivers. The monitoring of psychological distress using standardized questionnaires such as the Hospital Anxiety and Depression Scale (HADS) is therefore recommended. Caregiver burden questionnaires are used more often in clinical practice compared to distress questionnaires since they provide insight in the broader caregiver situation. These questionnaires can also be used for monitoring. An increase in scores on the monitor instrument should be discussed with the caregiver. Together with the caregiver, the professional can explore what kind of support is needed.

6. *Monitor cognitive and behavioral changes in patients with ALS or PMA and provide psychoeducation and support with regard to these changes*
   Behavioral problems in patients are related to both caregiver burden and psychological distress. Many caregivers are still unaware of the fact that cognitive and behavioral changes are common in patients with ALS or PMA. Behavioral changes such as apathy or increased irritability are often interpreted as patients' struggles to deal with the diagnosis, while these can be symptoms of the disease. Understanding these changes in patients and receiving advice on how to deal with these changes may lower psychological distress and caregiver burden in caregivers.

7. *Proactively inform caregivers about support options early in the disease course and repeatedly thereafter*

   Caregivers are often not aware that they are entitled to support. Information about support should be offered early in the disease course and since the needs and the situation changes over time, support options need to be offered repeatedly thereafter. For caregivers, it is often unclear what the support options exactly contain. For example, caregivers do often not fully know what kind of support a social worker or psychologist offers. Concrete examples of the specific topics that can be covered in support and case examples may help caregivers to get a better understanding of the options for support. This may help them recognize when they can benefit from the support options.

8. *Provide different support options*

   Needs of caregivers vary over time and between caregivers which indicates that different support options are needed. Caregivers express support needs with regard to 'more personal time', 'assistance in applying for resources', 'counseling', and 'peer contact'. Each multidisciplinary ALS care teams should offer support options with regard to these topics such as individual counseling, education on a website, a café for peer contact or an app with tips and advices form of other caregivers in line with the needs of caregivers.

9. *Support caregivers in how to deal with specific difficult situations*

   Caregivers might need different coping strategies to deal with the complex caregiving situations. Asking caregivers about the situations they struggle with and providing tools focused on how they can deal with their specific difficult situation may relieve stress and can help these caregivers to constructively deal with stressful situations in the future.

10. *Apply e-health in care*

    E-health seems to be an attractive tool in order to reach out to this target group. For some caregivers e-health seems to be the only manner to receive support, since they can not leave the patient alone. Caregivers of people with ALS of PMA are open for the use of e-health in care. In the further development of support options (e.g. dealing with behavior changes) the use of e-health is recommended in order to improve the uptake of in caregivers. E-health could also be used to monitor the psychological distress and needs of caregivers.

Directions for further research

The majority of the research in caregivers of patients with ALS or PMA is focused on patient factors that could have a negative influence on the wellbeing of caregivers. However, since we are currently not able to influence these patient factors (e.g. physical functioning) the focus should be directed towards that what is needed to strengthen caregivers. There is a lack of research directed at personal factors of caregivers that may influence caregiver burden or psychological distress.[1] Research focusing on how caregivers can improve their feeling of control and which personal factors of caregivers are relevant to their feeling of control within this complex care situation, is recommended. Monitoring psychological distress and caregiver burden over a longer period of time could provide more knowledge about the course of these constructs over time, which is needed in order to provide optimal support for these caregivers.

During this research project it became clear that there are two other subgroups that require more attention from professionals: children and parents in families with ALS or PMA and people who lost their partner because of ALS or PMA. For parents and children there is limited information or support about living with ALS or PMA in a family situation available. Parents struggle with questions regarding the information they provide to their children and the roles of children in caregiving. Therefore, specific support for these vulnerable families is needed. Partners of patients with ALS or PMA express a need for support after the death of their partners in order to process the recent events and to reflect on their situation. Professional support should be offered to guide caregivers in this process. Since the general practitioner (GP) is the care coordinator during the terminal phase of the disease, sharing information between the GP, primary care and the multidisciplinary ALS care team is needed. Research is required to further identify the support needs with regard to these topics and to develop and evaluate support options.

Another important type of support that requires more research is peer support. Almost half of the caregivers expressed a need for peer support. However, it is unclear how and when peer support should be provided to caregivers in order to optimally benefit from this contact. Nowadays, multidisciplinary ALS care teams provide peer support in different ways (e.g. caregiver café, caregiver information evenings). With more information about the working ingredients of peer support, multidisciplinary ALS care teams can optimize and facilitate this kind of support. This might be beneficial for the wellbeing of caregivers.

For upcoming trials aimed at improving the wellbeing of caregivers, a thorough investigation of the working mechanism prior to the start of a RCT is recommended. For example N of 1 trials could be used to design the intervention more thoroughly. This can help to understand the working mechanism of an intervention in a range of different individuals prior to the evaluation of the effectiveness. Conducting N of 1 trials also enable researchers to adapt the intervention after receiving feedback of caregivers. This type of research may improve our understanding of

support for caregivers and will built an accumulate evidence base, before moving to the ultimate step of testing the effectiveness in a RCT. However, this type of research requires more time and money. A grant system that provides researchers with these resources is needed in order to conduct research on the underlying working mechanism within individuals before testing the intervention between individuals.

In this patient population, family members are very motivated to participate in any kind of research related to ALS or PMA. They are very eager to support research since they hope researchers will find a solution for the disease. Although this psychosocial study did not focus on finding a solution for the disease, this positive attitude towards research might have influenced the results. In our research, we might have included caregivers who were highly motivated to participate in research but not motivated to take part in a support program. This might have raised the intervention drop-out numbers. Furthermore, caregivers who are motivated to participate in research might be different from the caregivers who might benefit from a support program. Therefore we encourage to take this aspect of positive motivation into account in future research.

Conclusion

Caregivers play a crucial role in the lives of patients with ALS or PMA but over time their levels of distress increase. Although they experience different support needs with regard to 'more personal time', 'assistance in applying for resources', 'counseling', and 'peer contact', caregivers can be reluctant to express their needs. The wellbeing of the patients is their main priority. Therefore, acknowledging caregivers in their crucial role, monitoring their wellbeing, and proactively informing them about the available support options early in the disease process and repeatedly thereafter is important.

The demand and control model showed that both behavioral changes and feeling of control over caregiving are related to feelings of distress, while physical functioning is not. Monitoring cognitive and behavioral changes in patients, providing information about these changes, and supporting caregivers in dealing with the specific difficult situations caused by these changes, is needed. A focus in both research and care on how caregivers can increase their feeling of control and how they can be strengthened in dealing with their situation is recommended.

The support program developed in this study did not show effectiveness on the level of distress of caregivers but caregivers did evaluate the program positively. The program did improve their control over their thoughts and caregivers reported that the program helped them to gain control over the caregiving situation, to accept negative emotions and thoughts, to be there for their

partner and to feel acknowledged. These results, in combination with the lack of other proven effective interventions for these caregivers, suggest that this program can be offered to caregivers of patients with ALS or PMA who would like to receive support in their caregiving situation. This blended support program can be an option next to traditional face-to-face support and other support options aimed at the caregiver.

Support for caregivers should not be offered as a standard program, but should be adapted to the needs, preferences and situation of the caregivers. Caregivers should be able to choose when they would like to receive what kind of information or support. This option of choice is important in order to increase the feeling of control over their already complex situation.

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Summary

Amyotrophic Lateral Sclerosis (ALS) and Progressive Muscular Atrophy (PMA) are neurodegenerative and fatal disorders. Patients suffer from progressive wasting and weakness of muscles, which leads to the inability to speak, paralysis and respiratory failure. Approximately 50% of patients show cognitive or behavioral changes, next to their physical impairments. As a result, patients become dependent on their environment and the majority of the care tasks are provided by informal caregivers. Providing care can be intense and stressful and previous research showed that caregivers often experience feelings of psychological distress and caregiver burden. However, not all caregivers experience feelings of distress or burden. It is unclear which factors explain the development of distress and caregiver burden in these caregivers. The demand and control model suggests that caregiver wellbeing is determined by two dimensions; care demands and perceived control over caregiving. Caregivers who experience high demands in combination with a feeling of low control over caregiving are at risk for physical and psychological distress. Although it is clear that these caregivers are at risk, there is a lack of supportive interventions for these caregivers.

The overall aim of this thesis is to improve the support for caregivers of people with ALS or PMA in order to enhance their wellbeing. In this thesis we aim to 1) unravel which caregiver and patient factors are related to caregiver burden and psychological distress in caregivers of people with ALS or PMA; 2) increase knowledge about the support needs of caregivers of people with ALS or PMA; 3) develop a blended support program for caregivers of people with ALS or PMA and evaluate the support program both quantitative and qualitative.

Part 1 Factors related to caregiver burden and psychological distress

In **chapter 2** a systematic review was performed to obtain insight into factors associated with caregiver burden in caregivers of patients with ALS. A total of 25 studies were included in which quantitative relations between patient or caregiver factors and caregiver burden were assessed. The overall quality of evidence for factors was assessed using the Grading of Recommendations Assessment Development and Evaluation approach. High quality of evidence was found for the relation between caregiver burden and the patient factor 'behavioral impairments'. Moderate quality of evidence was found for the relations between caregiver burden and the factors 'feelings of depression' of the caregiver and 'physical functioning' of the patient. The remaining caregiver factors (feelings of anxiety, distress, social support, family functioning and age) and patient factors (bulbar function, motor function, and respiratory function, disease duration, disinhibition, executive functioning, cognitive functioning, feelings of depression and age) that were rated showed low to very low quality of evidence for their association with caregiver burden. In conclusion, higher caregiver burden is associated with patients' behavioral and physical impairments and caregivers' depressive feelings. This information can be used to identify caregivers at risk for caregiver burden. This review also identified a lack of research into personal factors of caregivers that could be related to caregiver burden and further research with regard to these factors was recommended.

In **chapter 3** the development of psychological distress in caregivers and the association between coping styles and psychological distress over time were examined. Fifty-four caregivers were followed over a period of 10 months in a randomized controlled trial (RCT) for patients in the early stages of ALS. Emotion-oriented, task-oriented and avoidance-oriented coping styles were measured. Results showed that caregivers' psychological distress increased each month with 0.24 points on the Hospital Anxiety and Depression Scale. The emotion-oriented coping scale was associated with psychological distress but did not influence the development of psychological distress over time. However, emotional coping and distress might represent overlapping constructs which might explain the relation between these factors. The avoidance-oriented coping style and the task-oriented coping style were not related to psychological distress. The overwhelming majority of caregivers indicated using all three coping styles to some degree. Therefore, focusing on one coping style in the support for caregivers seems to be too simplistic for the complex situations they face. People may require different coping strategies in different situations. Coaching caregivers in learning how to apply different coping strategies in different stressful situations might be beneficial for their wellbeing.

To investigate the applicability of the demand and control model to the caregiver situation in ALS or PMA, we undertook a cross-sectional study described in **chapter 4**. In this study we investigated how care demands (physical impairments and behavioral changes in patients) and control (perceived control over caregiving) influences psychological distress in caregivers of patients with ALS or PMA. Besides the direct effects from demand and control on caregivers' psychological distress, we also assessed whether perceived control over caregiving moderated or mediated the relation between demand and psychological distress. Results showed that more behavioral changes in the patient and lower perceived control over caregiving in caregivers were associated with higher levels of caregivers' psychological distress. Physical impairments of the patients were not related to caregivers' psychological distress. No moderation or mediation effects were found of perceived control over caregiving on the relationship between demand and psychological distress. This study highlighted that monitoring, psychoeducation and support with regard to behavioral changes in patients is needed. Perceived control over caregiving might be a good target for caregiver interventions.

Part 2 Support needs of caregivers

Chapter 5 describes the results of the qualitative study aimed at exploring the support needs of caregivers of patients with ALS. Individual semi-structured interviews were conducted with 21 caregivers. A total of four global support needs emerged: 'more personal time', 'assistance in applying for resources', 'counseling', and 'peer contact'. Despite their need for support, caregivers were reluctant to seek or accept support for themselves. They saw the patients' wellbeing as their main priority. This underlines that a proactive approach from health care professionals is essential in order to prevent psychological and physical health problems in caregivers of people with ALS

or PMA. Professionals should acknowledge the importance of the role of caregivers from an early stage, monitor their wellbeing and repeatedly offer support opportunities. This study further offers concrete targets for the development of interventions for these caregivers. Since caregivers expressed a need for support but also reported lack of time, e-health can be an option to receive support in a less time-consuming manner.

Part 3 A blended support program: ALS caregiver support

Chapter 6 presents the protocol of the RCT that investigated the effects of a blended psychosocial support program for partners of patients with ALS or PMA compared to a wait-list control group. The aim of the support program was to increase feelings of control over caregiving in order to diminish feelings of psychological distress in partners. The blended intervention was based on Acceptance and Commitment Therapy and consisted of 1 face-to-face contact, 6 online guided modules and 1 telephone contact. The online modules contained psychoeducation, psychological and mindfulness exercises, practical tips and information, and options for peer contact. Caregivers were guided through the program by a psychologist specially trained for the purpose of this study.

Chapter 7 presents the results of the RCT that evaluated the effectiveness of the support program described in chapter 6. A total of 148 caregiver-patient dyads were included in this study. Although caregivers evaluated the program positively, no significant differences between the intervention group and wait-list control group on psychological distress, caregiver burden or quality of life in caregivers were found. The psychosocial support program for caregivers did also not influence the quality of life or psychological distress in patients. A significant positive intervention effect was found on the intervening variable self-efficacy with regard to being in control over thoughts. Almost half of the caregivers did not complete the intervention. The most frequently reported reason for not completing the intervention was lack of time. We concluded that appropriate timing of this support program seems to be crucial for caregivers in order to benefit from the content. Optimal timing may differ per individual and is likely dependent on multiple patient and caregivers characteristics.

Insight into the experiences with the different components of the support program (program evaluation) and into what caregivers gained from following the program (mechanisms of impact) is provided in **chapter 8**. A total of 23 caregivers who were enrolled in the RCT that investigated the effectiveness of the support program (chapter 7) were interviewed. Caregivers perceived the different components of the program overall as beneficial but ambivalent reactions were expressed about the mindfulness exercises and the peer contact functions. The main mechanism of impact of the program that caregivers reported was that they became aware of their own situation. They further indicated that the program helped them to perceive control over their caregiving situation, to accept negative emotions and thoughts, to be there for their partner and to feel acknowledged in having an important role. Caregivers expressed the need for a

more personalized program with respect to the order and timing of the modules and wanted to continue the support program over a longer period of time.

Chapter 9, the general discussion, provides a brief overview of the main findings and a reflection on these main findings. The findings are discussed according to the three main aims of this thesis and this has led to the following 10 recommendations for the improvement of support for caregivers of people with ALS or PMA:

1. Acknowledge caregivers and standardize the provision of support for caregivers.
2. Be careful with the use of the Dutch word for 'caregiver' [mantelzorger].
3. Make time to see the caregiver privately**.**
4. Actively ask caregivers about their needs.
5. Monitor the wellbeing of caregivers.
6. Monitor cognitive and behavioral changes in patients with ALS or PMA and provide psychoeducation and support with regard to these changes.
7. Proactively inform caregivers about support options early in the disease course and repeatedly thereafter.
8. Provide different support options**.**
9. Support caregivers in how to deal with specific difficult situations.
10. Apply e-health in care.

Recommendations for further research are also described. With regard to future development of interventions for caregivers, we recommend a thorough investigation of the working mechanism of interventions. Further research into working mechanisms is needed in order to understand who can benefit from interventions. For example, N of 1 trials could be used to design the intervention more thoroughly. Furthermore, a shift of focus is needed in caregiver research, instead of focusing on patient factors that may influence caregiver wellbeing, we need to focus on personal factors of the caregiver that can be influenced. More research on how we can strengthen caregivers and how we can enhance their feeling of control during the disease course of the patient with ALS or PMA is needed.

We concluded that the support program developed in this study did not show effectiveness on the level of distress in caregivers but the program was positively evaluated by caregivers. The program did improve control over their thoughts and caregivers reported that the program helped them to gain control over the caregiving situation, to accept negative emotions and thoughts, to be there for their partner and to feel acknowledged. These results suggest that this blended support program can be considered as one of the support options available for caregivers of patients with ALS or PMA. Allowing caregivers to choose which module they follow at what time and which pace may increase the perceived benefits of the intervention.

Nederlandse samenvatting

Amyotrofische Laterale Sclerose (ALS) en Progressieve Spinale Musculaire Atrofie (PSMA) zijn neurodegeneratieve en fatale aandoeningen. Patiënten ervaren toenemende zwakte van spieren, wat leidt tot problemen bij het spreken, problemen bij de ademhaling en verlamming. Ongeveer 50% van de patiënten vertoont naast de fysieke klachten ook veranderingen in het denken of in het gedrag. Als gevolg hiervan worden patiënten afhankelijk van hun omgeving en de meerderheid van deze zorgtaken wordt uitgevoerd door naasten. Zorg verlenen aan een naaste kan intens en stressvol zijn; uit eerder onderzoek blijkt dat naasten vaak gevoelens van psychologische stress of overbelasting ervaren. Niet alle naasten ervaren echter deze gevoelens. Het is onduidelijk welke factoren ten grondslag liggen aan de ontwikkeling van psychologische stress en overbelasting bij naasten van mensen met ALS of PSMA. Het 'demand en control' model suggereert dat het welzijn van naasten wordt bepaald door twee dimensies; zorgeisen en de ervaren controle over het uitvoeren van de zorgtaken. Op basis van dit model wordt verwacht dat naasten waaraan hoge eisen worden gesteld met betrekking tot het verlenen van zorg en die een laag gevoel van controle ervaren over het uitvoeren van de zorgtaken, een verhoogd risico op het ervaren van fysieke en psychische problemen hebben. Ondanks dat het duidelijk is dat naasten van mensen met ALS of PSMA een verhoogd risico hebben op het ontwikkelen van psychische en lichamelijke klachten, is er een gebrek aan ondersteunende interventies voor deze naasten.

Het doel van dit proefschrift is het verbeteren van de ondersteuning voor naasten van mensen met ALS of PSMA om hun welzijn te verbeteren. In dit proefschrift willen we 1) ontrafelen welke naaste- en patiëntfactoren gerelateerd zijn aan overbelasting en psychologische stress bij naasten van mensen met ALS of PSMA; 2) kennis verzamelen over de ondersteuningsbehoeften van naasten van mensen met ALS of PSMA; 3) een ondersteuningsprogramma ontwikkelen voor naasten van mensen met ALS of PSMA en het ondersteuningsprogramma zowel kwantitatief als kwalitatief evalueren.

Deel 1 Factoren gerelateerd aan gevoelens van overbelasting en psychologische stress

In **hoofdstuk 2** is een systematisch literatuuronderzoek uitgevoerd om inzicht te krijgen in factoren die samenhangen met gevoelens van overbelasting bij naasten van patiënten met ALS. In totaal zijn 25 studies geïncludeerd waarin kwantitatieve relaties tussen naaste- en patiëntfactoren en overbelasting zijn beoordeeld. De kwaliteit van het bewijs voor deze relaties werd geclassificeerd met behulp van de 'Grading of Recommendations Assessment Development and Evaluation'. Er is een hoge kwaliteit van bewijs gevonden voor de relatie tussen gevoelens van overbelasting bij naasten en de patiëntfactor 'gedragsstoornissen'. Dit betekent dat naasten van patiënten met gedragsstoornissen meer gevoelens van overbelasting ervaren. Er is een matige kwaliteit van bewijs gevonden voor de relaties tussen gevoelens van overbelasting bij naasten en de factoren 'gevoelens van depressie' van naasten en 'fysiek functioneren' van patiënten. De overige naastefactoren (gevoelens van angst, psychologische stress, sociale ondersteuning, functioneren van het gezin, leeftijd) en patiëntfactoren (bulbaire functie, motorische functie,

ademhalingsfunctie, ziekteduur, disinhibitie, executief functioneren, cognitief functioneren, depressieve gevoelens, leeftijd), toonden een lage tot zeer lage kwaliteit van bewijs voor hun verband met gevoelens van overbelasting in naasten. De conclusie van dit onderzoek is dat een sterker gevoel van overbelasting bij naasten is gerelateerd aan fysieke- en gedragsmatige veranderingen van de patiënt en depressieve gevoelens van de naaste. Deze kennis kan in de klinische praktijk worden gebruikt om te identificeren welke naasten risico lopen op gevoelens van overbelasting. Dit onderzoek toonde tevens aan dat er nog weinig onderzoek is gedaan naar persoonlijke factoren van naasten zelf welke gerelateerd kunnen zijn aan gevoelens van overbelasting. Daarom wordt verder onderzoek met betrekking tot deze persoonlijke factoren aanbevolen.

In **hoofdstuk 3** werd de ontwikkeling van psychologische stress en de relatie tussen copingstijlen (de manier waarop naasten met een probleemsituatie omgaan) en psychologische stress op de lange termijn onderzocht bij naasten van mensen met ALS. Vierenvijftig naasten werden over een periode van 10 maanden gevolgd in een gerandomiseerd gecontroleerd onderzoek (RCT) voor patiënten in de vroege stadia van ALS. Emotiegerichte, taakgerichte en vermijdingsgerichte copingstijlen werden gemeten. De resultaten toonden aan dat de psychologische stress van naasten elke maand toenam met 0.24 punten op de Hospital Anxiety and Depression Scale. De emotiegerichte copingschaal was weliswaar gerelateerd aan psychologische stress, maar had geen invloed op de ontwikkeling van psychologische stress op de lange termijn. Hierbij dient wel opgemerkt te worden dat emotiegerichte coping en psychologische stress moeilijk van elkaar te onderscheiden constructen zijn en dat de overlap tussen deze constructen de relatie tussen deze factoren zou kunnen verklaren. De vermijdingsgerichte copingstijl en de taakgerichte copingstijl waren niet gerelateerd aan psychologische stress. De overgrote meerderheid van de naasten gaf aan alle drie de copingstijlen te gebruiken. Focussen op één copingstijl in de ondersteuning van naasten lijkt om deze reden te simplistisch voor de complexe situaties waarmee ze worden geconfronteerd. Mensen hebben misschien andere copingstrategieën nodig in verschillende situaties. Naasten coachen bij het leren toepassen van verschillende copingstrategieën in verschillende stressvolle situaties kan gunstig zijn voor hun welzijn.

Om de toepasbaarheid van het 'demand en control' model op de situatie van naasten van mensen met ALS of PSMA te onderzoeken, hebben we een cross-sectionele studie uitgevoerd, beschreven in **hoofdstuk 4**. In deze studie werd onderzocht hoe zorgeisen (lichamelijke beperkingen en gedragsveranderingen bij patiënten) en controle (ervaren controle over het uitvoeren van zorgtaken) psychologische stress in naasten van mensen met ALS of PSMA beïnvloeden. Naast de directe effecten van de zorgeisen en mate van ervaren controle over het uitvoeren van zorgtaken op psychologische stress, hebben we ook onderzocht of de mate van controle over het uitvoeren van zorgtaken een moderator of mediator is in de relatie tussen zorgeisen en psychologische stress. De resultaten toonden aan dat meer gedragsveranderingen bij de patiënt

en lagere ervaren controle over het uitvoeren van zorgtaken in naasten, werden geassocieerd met meer psychologische stress. Fysieke beperkingen van de patiënten waren niet gerelateerd aan psychologische stress in naasten. Er werden geen moderatie of mediatie effecten gevonden van controle over het uitvoeren van zorgtaken op de relatie tussen zorgeisen en psychologische stress. Deze studie benadrukt dat zowel het monitoren van gedragsveranderingen bij patiënten, als het bieden van psycho-educatie en ondersteuning met betrekking tot het omgaan met deze veranderingen van belang is. De ervaren controle over het uitvoeren van zorgtaken kan een goed aangrijpingspunt zijn voor interventies voor naasten.

Deel 2 Ondersteuningsbehoeften van naasten

Hoofdstuk 5 beschrijft de resultaten van de kwalitatieve studie gericht op het in kaart brengen van de ondersteuningsbehoeften van naasten van mensen met ALS. Individuele semi-gestructureerde interviews werden afgenomen bij 21 naasten. Er kwamen in totaal vier globale behoeften naar voren: 'meer persoonlijke tijd', 'ondersteuning bij het aanvragen van hulpmiddelen', 'psychologische ondersteuning' en 'contact met andere naasten'. Ondanks de behoefte aan ondersteuning waren naasten terughoudend om steun voor zichzelf te zoeken of steun te accepteren. Het welzijn van de patiënten was hun belangrijkste prioriteit en de eigen behoeften werden als ondergeschikt beschouwd. Daarom is het belangrijk dat professionals de rol van naasten in een vroeg stadium erkennen, hun welzijn monitoren en herhaaldelijk verschillende ondersteuningsmogelijkheden aanbieden. Een proactieve benadering vanuit de professionals in de gezondheidszorg is essentieel om te kunnen bijdragen aan de preventie van psychische en lichamelijke problemen bij naasten van patiënten bij ALS. Deze studie biedt verder concrete handvatten voor de ontwikkeling van interventies voor deze naasten. Omdat naasten behoefte hebben aan ondersteuning, maar ook een gebrek aan tijd ervaren, kan e-health een optie zijn om ondersteuning te ontvangen op een minder tijdrovende manier.

Deel 3 Een ondersteuningsprogramma: ALS naasten support

Hoofdstuk 6 presenteert het protocol van de RCT, waarin de effecten worden onderzocht van een psychosociaal ondersteuningsprogramma voor partners van patiënten met ALS of PSMA vergeleken met een wachtlijst controlegroep. Het doel van het ondersteuningsprogramma was het vergroten van het gevoel van controle over het uitvoeren van zorgtaken, om daarmee de psychologische stress bij partners te verminderen. De interventie was gebaseerd op Acceptatie en Commitment Therapie en bestond uit 1 face-to-face contact, 6 online begeleide modules en 1 telefonisch contact. De online modules bevatten psycho-educatie, psychologische- en mindfulnessoefeningen, praktische tips en informatie, en boden daarnaast mogelijkheden voor contact met andere naasten. Partners werden door het programma geleid door een psycholoog die specifiek getraind was voor het doel van deze studie.

Hoofdstuk 7 presenteert de resultaten van de RCT die de effectiviteit van het ondersteuningsprogramma evalueerde, welke is beschreven in hoofdstuk 6. In totaal werden 148 partner-patiënt koppels geïncludeerd in de studie. Hoewel naasten het programma positief hebben beoordeeld, zijn er geen significante verschillen tussen de interventiegroep en wachtlijst controlegroep gevonden op de psychologische stress, gevoelens van overbelasting en kwaliteit van leven van de naasten. Ook bleek het psychosociale ondersteuningsprogramma voor de naasten geen invloed te hebben op de psychologische stress of kwaliteit van leven van de patiënt. Een significant positief interventie-effect werd gevonden op de interventie variabele self-efficacy met betrekking tot controle over gedachten. Bijna de helft van de naasten voltooide de interventie niet. De meest gerapporteerde reden om de interventie niet af te ronden was een gebrek aan tijd. We hebben geconcludeerd dat de juiste timing van dit ondersteuningsprogramma cruciaal is om te kunnen profiteren van de inhoud. De optimale timing kan per individu verschillen en is waarschijnlijk afhankelijk van meerdere kenmerken van zowel de patiënt als de naaste zelf.

Inzicht in de ervaringen met de verschillende componenten van het ondersteuningsprogramma (programma evaluatie) en in de wijze waarop naasten baat hebben bij het programma (mechanismen van impact) wordt gegeven in **hoofdstuk 8**. In totaal zijn 23 naasten geïnterviewd die in de RCT waren geïncludeerd (hoofdstuk 7). Naasten waren over het algemeen positief over de verschillende onderdelen van het programma, maar ambivalente reacties werden geuit over de mindfulnessoefeningen en de functies voor contact met andere naasten. Het belangrijkste mechanisme van impact van het programma was volgens de naasten dat ze zich meer bewust werden van hun eigen situatie. Ze gaven aan dat het programma hen hielp om controle te ervaren over hun situatie, om negatieve emoties en gedachten te accepteren en om er voor hun partner te zijn. Daarnaast hielp het dat ze zich erkend voelden in hun rol en dat deze rol als belangrijk wordt gezien door zorgprofessionals. Naasten gaven aan dat ze een meer gepersonaliseerd programma met betrekking tot de volgorde en timing van de modules zouden willen. Ook gaven naasten aan dat zij het ondersteuningsprogramma voor een langere periode zouden willen voortzetten.

Hoofdstuk 9, de algemene discussie, geeft een kort overzicht van de belangrijkste bevindingen gevolgd door een reflectie op deze bevindingen aan de hand van de drie hoofddoelen van dit proefschrift. Dit heeft geleid tot de volgende 10 aanbevelingen voor het bieden van ondersteuning aan naasten van mensen met ALS of PSMA:

1. Erken naasten en standaardiseer de ondersteuning van naasten.
2. Wees voorzichtig met het gebruik van het woord mantelzorger.
3. Maak tijd vrij om de naasten privé te zien.
4. Vraag naasten actief naar hun behoeften.
5. Monitor het welzijn van naasten.

6. Monitor cognitieve- en gedragsveranderingen bij patiënten met ALS of PSMA en verstrek psycho-educatie en ondersteuning bij deze veranderingen.
7. Informeer naasten proactief en vroeg in het ziekteproces over ondersteuningsopties en herhaal dit.
8. Bied verschillende ondersteuningsopties.
9. Ondersteun naasten bij het omgaan met specifieke moeilijke situaties.
10. Pas e-health toe in de zorg.

Daarnaast beschrijft dit hoofdstuk aanbevelingen voor verder onderzoek. Voor de verdere ontwikkeling van interventies voor naasten, wordt meer onderzoek naar het werkingsmechanisme van interventies geadviseerd. Onderzoek naar werkingsmechanismen van interventies maakt het mogelijk om meer zicht te krijgen op voor wie en op welke moment de interventie geschikt is. N=1 studies kunnen bijvoorbeeld worden ingezet om interventies nog grondiger te ontwerpen en door te ontwikkelen. Bovendien is er een verschuiving van aandacht nodig in het onderzoek naar het welzijn van naasten. In plaats van onderzoek te richten op patiëntfactoren die het welzijn van naasten kunnen beïnvloeden, is het ook nodig om te onderzoeken welke te beïnvloeden persoonlijke factoren van naasten bijdragen aan het ontwikkelen van psychologische stress. Vervolgens is meer onderzoek nodig naar hoe we naasten kunnen versterken en hoe we hun gevoel van controle kunnen vergroten tijdens het complexe ziekteproces van hun naaste met ALS of PSMA.

We concludeerden dat het ondersteuningsprogramma dat in deze studie werd ontwikkeld geen effect had op psychologische stress van naasten, ondanks dat het programma wel positief door hen werd beoordeeld. Het programma heeft wel het gevoel van controle over hun gedachten verbeterd. Tevens meldden naasten dat het programma hen hielp om controle te krijgen over de zorgsituatie, om negatieve emoties en gedachten te accepteren, om er te zijn voor hun partner en om zich erkend te voelen. Deze resultaten suggereren dat het ondersteuningsprogramma zou kunnen worden beschouwd als één van de beschikbare ondersteuningsopties voor naasten van patiënten met ALS of PSMA. Om voordelen van de interventie te ervaren lijkt het van belang dat naasten zelf meer invloed kunnen uitoefen op welke module ze volgen, op welk tijdstip en in welk tempo.

Dankwoord

Dit proefschrift had niet geschreven kunnen worden zonder de bijdragen en steun van een groot aantal mensen die ik hier graag wil erkennen en bedanken.

Allereerst wil ik alle naasten en patiënten bedanken die hebben deelgenomen aan het onderzoek. Het verdient grote waardering dat jullie je zo actief inzetten voor deelname aan onderzoek tijdens deze kwetsbare periode in het leven. Tijdens de interviews en face-to-face contactmomenten heb ik veel deelnemers thuis bezocht. Jullie persoonlijke verhalen hebben mij extra gemotiveerd om mij in te zetten om de ondersteuning voor naasten te verbeteren.

Prof. dr. Visser-Meily, beste Anne. Je tomeloze inzet en gedrevenheid voor de revalidatiezorg is inspirerend. Ik heb veel geleerd van je kennis en visie met betrekking tot het ondersteunen van naasten. Je bent altijd bereikbaar voor vragen of dilemma's en dat heb ik als heel prettig ervaren. Bedankt voor het vertrouwen, je goede begeleiding en je betrokkenheid.

Prof. dr. van den Berg, beste Leonard. Ik heb veel bewondering voor de wijze waarop jij je inzet om ALS de wereld uit te helpen. Bedankt voor alle begeleiding en feedback die je hebt gegeven tijdens het schrijven van dit proefschrift. Met jouw verfrissende en kritische blik wist je mij steeds weer uit te dagen om een verbeterslag te maken in mijn artikelen.

Dr. Beelen, beste Anita. Dank voor je betrokkenheid en je scherpe blik. Van jouw brede kennis van onderzoek en al onze gesprekken hierover heb ik veel geleerd. Bedankt dat ik altijd bij je aan kon kloppen voor hulp. Ik heb erg genoten van onze fijne samenwerking.

Dr. Schröder, beste Carin. Wat heb ik veel van je geleerd. Jouw schat aan kennis van de psychologie en jouw brede ervaring vanuit de praktijk zijn ontzettend waardevol geweest voor dit onderzoek. We hebben tal van gesprekken gevoerd over psychologische modellen en de content van de interventie en na elk gesprek ben ik weer meer geïnspireerd geraakt. Naast al het harde werken was er ook altijd ruimte voor gezelligheid. Dank voor alles, jouw begeleiding en steun, de fijne samenwerking en alle leuke momenten.

De leden van de beoordelingscommissie, prof. dr. Notermans, prof. dr. Teunissen, prof. dr. Schoonhoven, prof. dr. Evers en prof. dr. Prinsen, wil ik graag danken voor het lezen en het beoordelen van mijn proefschrift.

Een aantal co-auteurs hebben ook een belangrijke bijdrage geleverd aan dit proefschrift. Stans, bedankt dat ik heb kunnen leren van alle bevindingen uit jullie waardevolle onderzoek. Ik heb genoten van de prettige samenwerking en je input heeft mij veel geholpen bij het opzetten en beschrijven van het onderzoek. Sigrid, door jouw brede kennis van kwalitatief onderzoek hebben we het kwalitatieve artikel naar een hoger niveau kunnen tillen. Veel dank hiervoor. Annerieke,

bedankt voor al het werk dat je hebt verzet voor onze gemeenschappelijke artikelen. Ik vond het heel fijn om jou als collega te hebben en met jou samen te werken.

Via deze weg wil ik Stichting ALS Nederland bedanken voor de subsidie die dit project mogelijk heeft gemaakt.

ALS Patients Connected, en in het bijzonder Ruud Kolijn en Conny van der Meijden, bedankt voor al jullie hulp. Jullie bereidheid om mee te lezen, feedback te geven of oproepen te delen heeft veel geholpen bij dit onderzoek en wordt zeer gewaardeerd.

Imke, wat hebben we hard gewerkt om alle deelnemers te benaderen en wat waren we blij met elke nieuwe aanmelding voor het onderzoek. Veel dank voor al je inzet. Marc, bedankt voor al je bijdragen en je betrokkenheid bij het onderzoek.

Julia, Janneke, Joost, Angelique, Anke en Eefke, jullie hebben geweldig werk verzet. Jullie waren ieder erg enthousiast en betrokken bij het project. Ik wil jullie ontzettend bedanken voor jullie belangrijke bijdragen en de prettige samenwerking.

Mijn collega's in het UMCU en van het Kenniscentrum, bedankt voor een hele leuke tijd. Door jullie was het altijd gezellig op de afdeling en tijdens congressen of uitjes. Ik wil specifiek ook even het lunchgroepje van onderzoekers in het UMCU bedanken, de goede gesprekken (en de talloze slechte grappen) tijdens de lunch waren een welkome onderbreking. Leonhard, wat hebben wij veel koffie gedronken samen. Jij was er altijd om te sparren, te lachen of om successen te vieren. Ook was het fijn om met jou te werken aan artikelen. Bedankt voor alle leuke momenten en je steun. Vincent, jij stond altijd voor mij klaar bij dilemma's of bij een writers' block. Daarnaast ben je altijd in voor gezelligheid. Bedankt voor je support en voor de leuke tijd. Mia en Nanda, wat een mooie app is er opgeleverd, iets om trots op te zijn. Bedankt voor de fijne samenwerking!

Daarnaast gaat ook veel dank uit naar mijn familie en vrienden, een aantal wil ik in het bijzonder noemen:

De vriendengroep, voor jullie was het soms onduidelijk wat ik nu precies deed en dit heeft tot verwarrende en hilarische gesprekken geleid. Toch bleven jullie geïnteresseerd in mijn werk. Bedankt voor alle gezelligheid en leuke momenten samen. Het is weer tijd voor een feestje. Iris en Bianca, bedankt voor alle lachsessies, goede gesprekken en lekkere etentjes. Ik hoop dat het team altijd blijft bestaan, het wordt wel tijd voor een nieuwe naam. Linda, Muriël en Jitske, sinds onze studie verliezen we elkaar niet meer uit het oog. Bedankt voor al jullie interesse in mijn onderzoek, jullie support en voor de gezelligheid. Jullie zien geeft mij altijd energie. Sharon, onze vriendschap is waardevol voor mij. Bedankt voor je luisterend oor, alle gezellige etentjes en je steun.

Lieve familie Kroeb en Schaap, bedankt voor jullie interesse in mijn werk en voor alle gezellige momenten die we samen hebben. Ik geniet altijd erg van onze etentjes, vakanties, familiedagen en uitjes.

Lieve Opa en Oma, bedankt dat jullie mij bewust hebben gemaakt van het feit dat studeren een voorrecht is. Met jullie positieve instelling en oneindige liefde voor elkaar zijn jullie grote voorbeelden voor mij.

Lieve Papa en Mama, wat heb ik toch een geluk met jullie. Jullie onvoorwaardelijke steun en geloof in mijn kunnen, betekenen zoveel voor mij. Bij jullie zijn, voelt nog altijd als thuiskomen. Bedankt voor alles.

Menno en Mariska, ik geniet van onze momenten samen en ben erg blij met onze sterke band. Of het nu gaat om advies of om een drankje, ik kan altijd op jullie rekenen. Onze tripjes naar Rome, Londen en Krakau waren fantastisch! Bedankt voor het meedenken en steunen de afgelopen jaren.

Mijn paranimfen Tamara en Linda, wat ben ik trots dat jullie vandaag naast mij staan. Lieve Tam, jij kent mij zo goed dat een blik vaak voldoende is. Je bent een fantastische vriendin en het is altijd zó fijn om je te zien. Bedankt dat je er altijd voor mij bent. Lieve Lin, wat ben je een belangrijke steun. Het is zo prettig om altijd bij je terecht te kunnen. Samen met Ferris en Owen bood je de perfecte afleiding op stressvolle dagen. Ik geniet van elk moment met jullie! Bedankt voor alles.

Lieve Jeroen, bedankt voor al je liefde en steun. Samen met jou zijn, maakt elke dag een stukje mooier.

Curriculum Vitae

Jessica de Wit werd geboren op 22 maart 1988 in Hoorn. Na het voltooien van het gymnasium aan het Martinus College in Grootebroek, studeerde zij psychologie aan de Vrije Universiteit van Amsterdam. Zij koos tijdens haar studie voor de afstudeerrichting klinische psychologie. Tijdens haar onderzoeksstage op de afdeling Klinische psychologie aan de Vrije Universiteit van Amsterdam ontstond haar interesse voor toegepast onderzoek. Tijdens deze stage werkte zij mee aan onderzoek naar het effect van een online interventie voor mensen met insomnia en daarna bleef zij op dit project werkzaam als onderzoeksassistent. Na het afronden van haar studie werd zij aangesteld als junior onderzoeker en verrichte zij onder andere onderzoek naar online ondersteuning voor mensen met chronische psychiatrische klachten en mensen met een verstandelijke beperking. In december 2014 startte Jessica als promovenda op de afdeling Revalidatie, Fysiotherapiewetenschap en Sport van het Universitair Medisch Centrum Utrecht. Hier verrichtte zij onderzoek naar het ondersteunen van naasten van mensen met Amyotrofische Laterale Sclerose en Progressieve Spinale Musculaire Atrofie wat resulteerde in dit proefschrift. Sinds april 2019 is Jessica bij de gemeente Den Helder aangesteld als regionaal projectleider aanpak huiselijk geweld en kindermishandeling binnen het landelijke project "Geweld hoort nergens thuis".

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