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Treatment effect modifiers for the Patient Education Program for Parkinson’s disease

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Abstract

Aim: A recent randomized controlled trial showed significant benefits for PD caregivers' psychosocial problems and need for help and a trend towards significant improvement of patients' quality of life after participation in the Patient Education Programme for Parkinson's disease (PEPP). Large variations in change scores were found, indicating variation in benefit. The aim of this study is to search for treatment effect modifiers.

Methods: Outcome measures were patients' quality of life (PDQ-39) and caregivers' psychosocial burden (BELA-A-k). Candidate treatment effect modifiers were participants' characteristics and baseline scores on psychological questionnaires (BELA-P/A-k, PDQ-39, EQ-5D, SDS) and patients' neuropsychological test scores (MMSE, DART, WT, BADS rule shift, TMT, Stroop). Secondary analyses of data from a randomized controlled trial with 64 patients and 46 caregivers were performed by means of regression analyses with treatment group interaction terms.

Results: No significant modifiers were found for the patients. In the caregiver group, a higher MMSE score of the patient at baseline was found to be a significant predictor of a lower BELA-A-k Bothered by score post-intervention of the caregiver.

Conclusions: A potential predictor of treatment benefit was found for caregivers of PD patients with better cognitive functioning. This study did not find treatment effect modifiers for PD patients: demographics, disease stage and time of diagnosis, cognitive functioning, level of baseline psychosocial burden, participating with or without a caregiver, and caregiver changes did not influence treatment outcome. The Patient Education Programme for Parkinson's disease seems suitable for the majority of the patients.

Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative diseases; it has an incidence over the age of 65 of about 160 per 100 000.[1] The core features of the disease are a resting tremor, rigidity, bradykinesia/akinesia and postural disturbances. Cognitive deficits and neuropsychiatric problems are common. Often, PD has a substantial adverse impact on psychosocial wellbeing and quality of life.[2] Increased psychosocial problems and depressive symptoms are associated with greater decline of Qol over time and are therefore often recommended to be included in PD treatment.[3,4] Caregivers provide most of the care for PD patients with adverse effects on their own wellbeing.[5]

The Patient Education Programme for Parkinson's disease (PEPP) is a standardized psychosocial intervention directed at both patients and caregivers. It is aimed at educating and training PD patients and caregivers skills to cope with psychosocial consequences of PD in order to improve their quality of life. The PEPP has been evaluated on its feasibility in seven European countries[6,7] and is thereafter standardized in a manual, available in six languages, including Dutch and English.[8,9] After the formative evaluation, a randomized controlled trial has been performed to assess its effectiveness.[10] It was found that after participation in the programme, caregivers reported a significantly decreased psychosocial burden and need for help. In the patients group, a trend towards significant improvement of quality of life was found. Large variations were found in change scores from pre- to post-intervention. Participants do not benefit equally from participation in the programme. It has not been investigated yet whether participants with specific characteristics benefit more. Characteristics that identify subgroups of patients who respond differently to a specific intervention are called treatment effect modifiers. A first hypothesis is that impaired cognitive functions, like impaired memory may hamper patients in learning the skills taught within the programme. Also, self-regulating abilities, like planning and cognitive flexibility may be necessary to implement knowledge and skills in daily practice. A second interest is the influence of baseline level of psychosocial burden of participants. Some studies report more benefits in patients with more psychological problems, others report more benefits in well-adjusted patients.[11] In a recent meta-analysis on psychosocial interventions in cancer patients, it was concluded that effectiveness of interventions increased when applied to patients with more psychological distress.[12] At last, a mutual influence between patient and caregiver characteristics and benefits is expected. It is also likely that the programme may be less effective for a patient alone versus a patient in the presence of a partner also receiving this intervention. In a meta-analysis on psychosocial interventions it was found that involving a family member (often the spouse) achieved reductions in patient depression.[13]

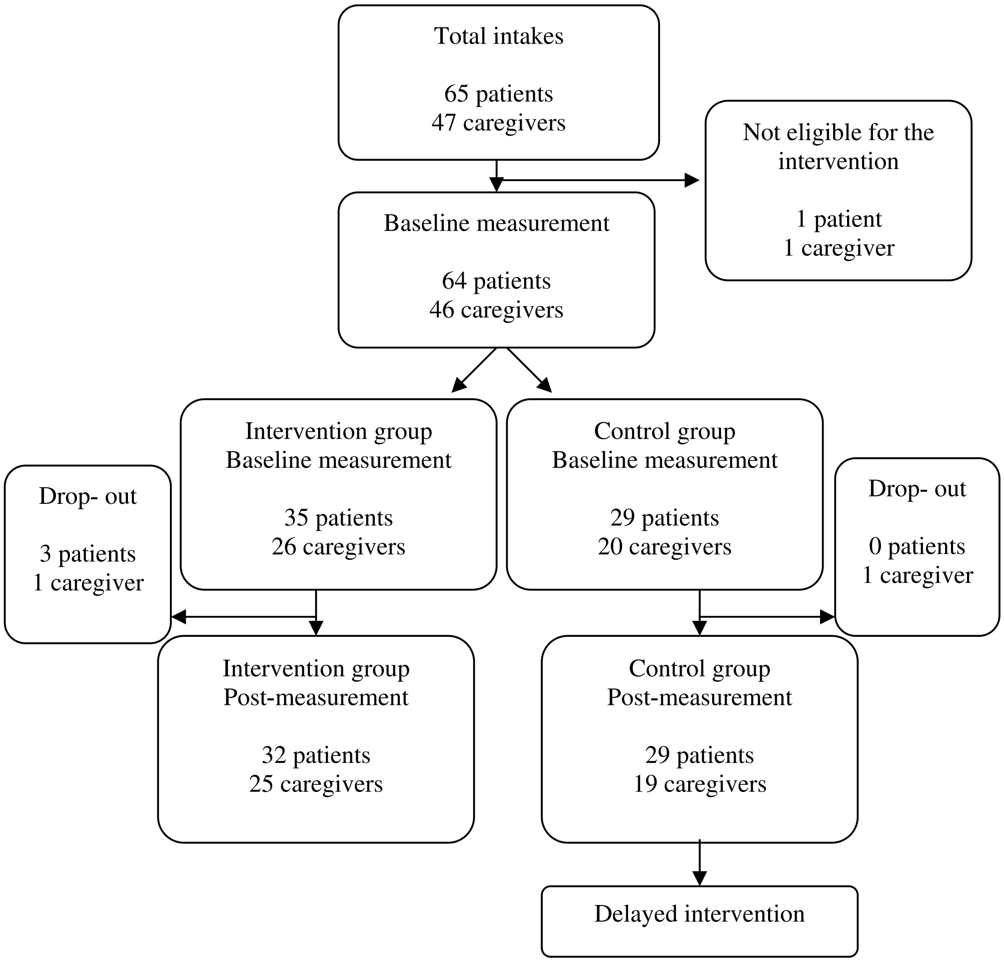
Information about treatment effect modifiers could be helpful to improve referring advices for participation in the programme. The (cost) effectiveness of the intervention may increase if it can be selectively provided for those who benefit most.[14] Therefore the aim of this study is to search for treatment effect modifiers by means of secondary analyses of data from our randomized controlled trial in which PD patients as well as the caregivers participated in the programme.[10]

Methods

Participants

Sixty-five patients were recruited via the outpatient neurological department of the Leiden University Medical Centre, by means of an advertisement in a regional newspaper, and during meetings of the patient lay organisation. All patients had to fulfil the following criteria: 1) idiopathic Parkinson's disease; 2) no currently intensive psychiatric treatment. Caregivers were also eligible for the study as was participation without partner. Patients were requested not to change their medication during the study. One patient and one caregiver were excluded because of severe psychiatric problems. Eventually, 64 patients and 46 caregivers were allocated to either the intervention group or the control group. For the flow-diagram of the sample see Figure 1. The medical ethical committee of the LUMC approved the study. All participants gave their informed consent.

Figure 1 Flow diagram of the sample



Procedure

Participants were randomized after the baseline assessment to either the intervention or to the control group. Patients in the intervention group participated in the PEPP, consisting of eight weekly sessions of ninety minutes duration. Trainers followed the detailed standardized manual.[8,9] For a summary of its contents, see A'Campo.[7,10] The PEPP comprises a separate but parallel programme for patients and their caregivers (5-7 participants per group). Patients could also participate without a caregiver. The programme's key element includes techniques from the cognitive behavioural therapy, like cognitive restructuring, systematic relaxation training, situational behavioural analysis and training in social skills. The control group received usual care and no PEPP intervention during the study, but they received the intervention after finishing the follow-up measurement (delayed intervention group).

Assessments

Of all participants, demographic data were recorded. The Hoehn & Yahr scale[15] was measured to assess disease stage.

The following neuropsychological tests were administered by a trained research associate in a fixed order: Mini Mental State Examination (MMSE);[16] the National Adult Reading Test, Dutch version (DART);[17] Rey's Auditory Verbal Learning Test (Word Test, WT);[18] Rule Shift Card test from the Behavioural Assessment of the Dysexecutive Syndrome (BADS ,part 1 and 2);[19] Trail Making Test (TMT A and B);[20] and the Stroop Colour Word Test, part I, II and III.[21]

The following self-report questionnaires were used. The impact of psychosocial problems due to PD and need for help were assessed by the 'Belastungsfragebogen Parkinson kurzversion' (BELA-P-k),[22] proving a 'Bothered by' and 'Need for help' score. For the caregivers, the caregiver version was used: the 'Belastungsfragebogen Parkinson Angehörigen kurzversion (BELA-A-k).[23] The quality of life (Qol) of the patients was assessed by the Parkinson's Disease Questionnaire (PDQ-39),[24] providing a Summary Index (SI). In the caregivers, Qol was assessed by the Dutch version of the EuroQol-5D (EQ-5D).[25] The Self-rating Depression Scale (SDS)[26] was used to measure depression in both patients and caregivers. Measurements were performed within two weeks before and within one week after participation in the PEPP.

Statistical analysis

The data were analyzed with the Statistical Package for the Social Sciences (SPSS 16.0). Differences in baseline demographics and clinical variables between the two randomized treatment groups were analyzed by means of independent sample-t-test or Chi Square tests if appropriate. Patient and related caregiver data were combined to assess mutual influences. To assess if treatment assignment modified associations of the outcome measures with candidate modifiers, linear regression analyses (method = enter) were performed for each candidate predictor separately. In these models, the post-intervention scores on PDQ-SI in the patients and on BELA-A-K Bothered-by scale in the caregivers served as the dependent or outcome variables. The interaction terms of each candidate predictor with the randomized treatment groups dummy (PEPP intervention group versus control group) served as the independent predictor, along with the pre-intervention scores to adjust for baseline scores and along with constituent main effects. In case of more than one significant predictor of treatment effect size, a backward deletion regression model was to be performed to search for the best predictive model. At last, significant treatment modifiers will be inserted into regression analyses for each possible value of the variable to search for which scores treatment effect is significant.

Results

Demographics and clinical baseline characteristics of the intervention and control group are reported in Table 1. Sixty-one patients and 44 caregivers completed post-intervention assessment (Figure 1). The effects found in the RCT are presented in Table 2 as published earlier.[10] The regression analyses per candidate predictor are given in Table 3. Patients' MMSE score at baseline was found to be a significant predictor of caregivers' BELA-A-k Bothered by score post-intervention ($p = 0.05$). A higher score on patients' MMSE, indicating better global cognitive functioning, predicted better treatment outcome regarding caregivers' psychosocial burden after participation in the programme. The intervention effect was significant from MMSE score ≥ 28. No significant modifiers were found for the patients.

Table 1 Demographics and clinical characteristics of the intervention and control group

	Patients		Caregivers	
	Intervention group (*n* = 35)	Control group (*n* = 29)	Intervention group (*n* = 26)	Control group (*n* = 20)
Men/women, *n*	20/15	15/14	9/17	8/12
Age (Yrs)	65.5 (8.9)	64.2 (9.1)	63.4 (8.4)	61.5 (11.3)
Partner/single, *n*	30/5	24/5	26/0	20/0
Education level, *n*				
Till age of 18/higher	18/17	13/16	14/12	12/8
Employed/not, *n*	8/27	8/21	8/18	6/14
Diagnosis since (Yrs)	5.95 (5.33)	5.46 (4.45)	-	-
Hoehn & Yahr	2.4 (1.0)	2.3 (0.7)	-	-
ADL scale	76.0 (18.8)	78.9 (15.1)	-	-
SDS	54.4 (9.4)	51.6 (8.7)	43.3 (10.7)	45.0 (8.1)
No/min./mod./sev., *n*	9/16/7/2	13/13/0/2	18/6/1/0	17/1/2/0
MMSE	27.4 (3.4)	28.8 (1.1)	28.9 (1.1)	28.8 (1.7)
DART	107.4 (2.2)	107.5 (12.4)	-	-
Word test[1]			-	-
- Immediate	33.1 (11.5)	36.3 (8.5)		
- Delayed	5.5 (3.2)	6.6 (2.7)		
- Recognition	26.2 (3.1)	27.8 (1.8)		
Stroop III[2]	49.2 (10.1)	50.3(9.8)	-	-
Trail making Test B[3]	52.7 (13.8)	51.2 (12.6)	-	-
Rule shift II[4]	3.2 (3.7)	2.3 (2.9)	-	-
PD medication, *n*	31	25		
Antidepressants, *n*	6	3		
Benzodiazepines, *n*	4	2		

Values are mean (SD) unless otherwise indicated. Tests are independent t-test, unless otherwise indicated. † Chi-square test

Abbreviations: Yrs, years; ADL, Activities of Daily Living scale; SDS, Self-Rating Depression Scale; min., minimal; mod., moderate; sev., severe; MMSE, Mini Mental State Examination; DART, National Adult Reading Test, Dutch version; IQ, intelligence quotient.

1 The number of correct words was used; 2 The T (interference) score was used corrected for Stroop card II, age and education; 3 The T score was used corrected for TMT card A, age and education; 4 The number of errors on task II was used.

Table 2 Effects found as published in the previous randomized controlled trial[10]

		Intervention group Mean change	Control group Mean change	*p*
Patients	PDQ-39 SI	(*n* = 29)	(*n* = 28)	
		3.07 (7.81)	-1.79 (6.73)	0.015
Caregivers	BELA-A-k	(*n* = 21)	(*n* = 15)	
	Bothered by	2.25 (5.41)	-4.80 (6.66)	0.001*
	Need for help	5.05 (9.03)	-6.33 (8.37)	0.001*

PDQ-39 SI, Parkinson's Disease Questionnaire Summary Index; BELA-A-k, Belastungsfragebogen Angehörigen kurzversion.

* significant with Bonferoni adjustment for multiple comparisons.

Table 3 Regression analyses per candidate predictor of treatment effect size

	Post-treatment PDQ-39 SI Patients (*n* = 61)	Post-treatment BELA-A-k BB Caregivers (*n* = 44)
	β (SE)	*β* (SE)
Gender	0.5 (3.8)	-5.1 (3.8)
Age	-0.1 (0.2)	-0.1 (0.2)
Education level	-4.3 (2.6)	1.4 (3.8)
Participation with caregiver	1.2 (4.4)	-
Time of diagnosis patient	-0.5 (0.4)	-
Hoehn & Yahr score patient	0.8 (2.4)	0.0 (0.0)
Cognitive functioning patient		
- MMSE	1.9 (1.3)	**-2.8 (1.4)***
- DART	-0.0 (0.0)	0.0 (0.0)
- Word test[1] -Delayed	-0.1 (0.7)	0.6 (0.7)
-Recognition	-0.1 (0.9)	0.8 (0.8)
- Stroop III[2]	-0.1 (0.2)	-0.0 (0.2)
- Trail making B[3]	0.1 (0.1)	-0.0 (0.0)
- Rule shift II[4]	0.2 (0.5)	-0.1 (0.6)
Baseline PDQ-SI patient	-0.2 (0.2)	0.2 (0.1)
Baseline EQ-5D caregiver		
- Utilities	15.2 (15.7)	9.3 (10.9)
- VAS	-0.0 (0.1)	0.1 (0.2)
Baseline SDS patient	-0.1 (0.2)	-0.2 (0.2)
Baseline SDS caregiver	-0.4 (0.3)	0.2 (0.2)
Baseline BELA-P-k patient		
- BB	0.1 (0.2)	0.1 (0.2)
- NFH	-0.1 (0.2)	0.0 (0.2)
Baseline BELA-A-k caregiver		
- BB	-0.2 (0.3)	-0.2 (0.2)
- NFH	-0.1 (0.2)	-0.2 (0.2)
Change PDQ-SI patient	-	-0.4 (0.2)
Change BELA-A-k BB caregiver	-0.4 (0.5)	-

Abbreviations: PDQ-39 SI, Parkinson's Disease Questionnaire Summary Index; BELA-A-k BB, Belastungsfragebogen Angehörigen kurzversion Bothered By scale; MMSE, Mini Mental State Examination; DART, National Adult Reading Test, Dutch version; EQ-5D, Euro-Qol 5 dimensions; VAS, Visual Analogue Scale; SDS, Self-Rating Depression Scale; BELA-P-k, Belastungsfragebogen Parkinson kurzversion; BB, Bothered By scale; NFH, Need for Help scale. * p = 0.05, considered as significant.

The β shown is the regression coefficient of the interaction term of a candidate predictor with the treatment group, and is interpreted as the increase in treatment effect in the intervention group per unit increase of the predictor.

1 The number of correct words was used; 2 The T (interference) score was used corrected for Stroop card II, age and education; 3 The T score was used corrected for TMT card A, age and education; 4 The number of errors on task II was used.

Table 4 Treatment effect of the caregiver per MMSE score of the patient

MMSE score of patient	Treatment effect on BELA-A-k of caregiver P value (95% CI)
30	0.001 (-15.8 - -4.2)
29	0.001 (-11.2 - -3.1)
28	0.031 (-8.2 - -0.4)
27	0.583 (-7.1 – 4.0)
26	0.735 (-6.6 – 9.2)

Abbreviations: MMSE, Mini Mental State Examination; BELA-A-k, Belastungsfragebogen Angehörigen kurzversion; CI, confidence interval.

Discussion

The Patient Education Programme seems suitable for the majority of the patients, regardless of their level of cognitive functioning, baseline psychosocial burden and having a participating caregiver, since no significant treatment effect modifiers were found in the patients group. Also, gender, age, education level, disease stage and time of diagnosis, baseline scores, and caregiver changes were not of influence. We did find one significant predictor for caregiver treatment outcome: better global cognitive functioning of the patient as measured with the Mini Mental State Examination (MMSE) predicted better caregiver treatment outcome regarding psychosocial burden. Caregivers of patients with better cognitive functioning seem to benefit more from the programme, independently of the disease stage (measured with the Hoehn and Yahr scale). Treatment effect was significant for caregivers of patients' with a MMSE score ≥ 28. For caregivers of patients with more cognitive problems or dementia, no significant benefit (but neither an unfavourable effect) was found. This was against expectation, because caregivers of patients with more cognitive problems experience caregiver burden the most and therefore especially seem to need psychosocial help (27). However, reduced benefit for dementia caregivers participating in psychosocial interventions has been found in a meta-analysis.[28] In that study it was hypothesized that dementia caregivers have to cope more with unpredictable and uncontrollable stressors, like personality changes in the patient, which may hamper them from benefitting from the coping strategies in psychosocial interventions.[13,28] Individual interventions may be more effective above group interventions for this particular caregiver Group.[29]

In our study sample of patients (MMSE range of 17-30), we did not found that patients with more cognitive problems benefited less from the programme. Therefore, patients with dementia or some cognitive problems should not be excluded from participation. However, it is likely that there will be a boundary level for cognitive functioning, since severely demented patients will not be able to participate. A study with more severely demented PD patients may reveal what these limits are.

Patient and caregiver demographics (gender, age, education level) and patient clinical characteristics (time since diagnosis, disease stage) were not predictive in both patients and caregivers. However, a more complex association may exist. It might be that time since diagnosis/disease stage is related to treatment outcome in a u-shaped manner. In our study, the clinical experience was that recently diagnosed patients often found it quite overwhelming and confronting to participate and patients who are more invalidated found it more burdensome. Future research may explore this hypothesis. In a study of Nolte regarding the effectiveness of chronic disease self-management courses, greater benefits for participation have been found for younger women.[30]

Furthermore, against expectation, no predictive value of baseline psychosocial burden was found as measured by several questionnaires. It was expected that patients with more psychosocial burden would have more opportunity to improve. Baseline scores of the outcome variables did significantly predict post-intervention scores within the intervention group, however not more than in the control group (non-significant interaction terms). This is in contrast with a recent meta-analysis on psychosocial interventions in patients with cancer, it was concluded that effectiveness of interventions increased when applied to patients with more psychological distress.[12]

Participation with or without a caregiver was no predictor for patient outcome. This indicates that patients alone can achieve equal effects compared to patients with participating caregiver. Randomly allocating patients in future research can reveal the importance of a parallel caregiver programme. In other studies, surplus value of involving a caregiver has been found in treating depression in patients.[13] Participation of the spouse may be experienced by the patients as an act of support. Moreover, regardless of the value of a participating caregiver for the patient, the programme has clear benefits for caregivers themselves as significant reduction of psychosocial burden and need for help has been found.[10] We did not found that change in patient outcome was predictive for change in caregiver outcome and vice versa. We did expect a mutual influence, because better psychological wellbeing of the PD patients is associated with less caregiver distress.[27]

Some limitations of the study have to be considered. First of all, MMSE scores of the patients were predictive for caregiver outcome, however, other neuropsychological test scores were not, which is not consistent. Secondly, sample size was relatively small. This may have resulted in the large confidence intervals, indicating that the findings are compatible with a wide range of effect sizes, and making it necessary to interpret the result carefully. Therefore, the treatment effect modifier found in this study should be externally validated in a study with larger sample before the exclusion of caregivers of patients with more cognitive problems from the programme will be incorporated in guidelines for clinical practice. Furthermore, the relatively small sample size could have resulted in the lack of significant modifiers for treatment outcome in the patients and caregivers. Also, more treatment effect modifiers can be of interest in future research, like motivation and degree of commitment, self-efficacy and personality. Motivation is likely to be an important factor for treatment success.

In conclusion, we found a potential predictor for treatment benefit for caregivers of patients with better cognitive functioning. This study did not find treatment effect modifiers for PD patients: demographics, disease stage and time of diagnosis, cognitive functioning, level of baseline psychosocial burden, participating with or without a caregiver, and caregiver changes did not influence treatment outcome. The Patient Education Programme for Parkinson’s disease seems suitable for the majority of the patients.

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